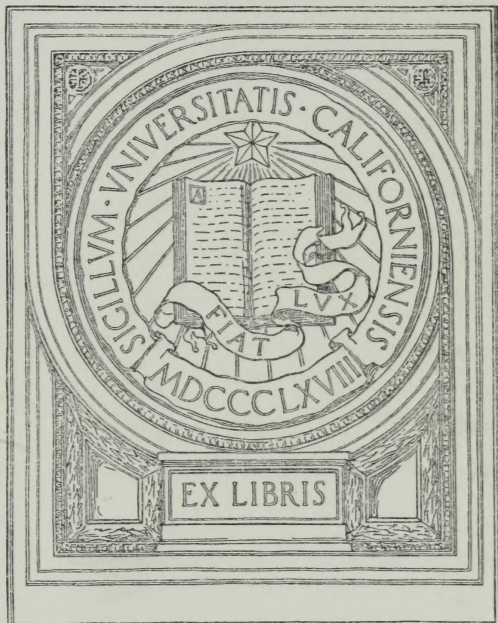


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HUMAN PATHOLOGY

A TEXTBOOK

BY

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CLEVELAND, OHIO.

WITH AN INTRODUCTION BY

SIMON FLEXNER, M. D.

20 ILLUSTRATIONS IN COLOR AND 443, BLACK AND WHITE

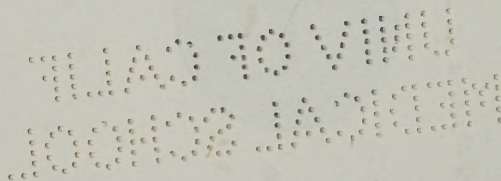


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AT THE WASHINGTON SQUARE PRESS
PHILADELPHIA, U. S. A.

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TO MY WIFE

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PREFACE

THE history of pathology shows a gradual evolution from a subject based almost entirely on morphology to one so comprehensive that as H. R. Dean says, "to the pathologist—all medical things are pathology." From this point of view clinical medicine is applied pathology. At any rate, pathology is no longer merely the study of morbid form, although no evolution or development can divorce from it the fundamental importance of pathological anatomy. The purpose of this book is to present the morphological alterations incident to disease, in the light of modern views as to their functional significance. The subject matter is confined to human pathology, since the work is designed for students and practitioners of medicine, but general biology has been called upon to furnish data relevant to the origin, course and natural history of disease as it affects man. The features of morbid anatomy and histology are studied objectively and are looked upon as established facts. At the present time, explanations of disease and interpretations of its phenomena are often hypothetical and the attempt is made in the discussions to distinguish clearly between fact and theory. A working knowledge of normal anatomy and physiology and of bacteriology is prerequisite to a comprehension of pathology. These subjects are correlated with the processes and products of disease and, with the more important topics, the whole concept is employed as a basis for a brief introduction to the clinic. In summary this is a textbook of pathological anatomy and histology, related to the broader functional aspects of disease.

A textbook is only an introduction to the essentials of a subject. References may be given to the literature, but, in view of the rapid advances of biological and medical research, only by observation, investigation and well directed reading can the subject matter be kept abreast of the times. An important part of education is acquaintance with the names of those who have furnished its heritage. In the earlier chapters the names of investigators are given in the text infrequently and the student can get the references from the list at the end of each chapter. Later, however, as greater familiarity with the subject is assumed, the names are inserted more freely. In so far as possible references are made to journals easily accessible and in the English language. The bibliography is in no sense complete, but is so selected that by its use an introduction to the literature of pathology may be gained. The mode of reference is in accord with that of the American Medical Association.

The conventional division into general and special pathology has been adopted as the result of a long teaching experience. It is believed that this arrangement is in harmony with the position of pathology in the medical curriculum and best serves to present the subject as an introduction to, and a

basis for, the clinical branches. For the advanced student and the practitioner it affords convenience of reference.

At the beginning of each chapter in general pathology the factual material is arranged in tabular form so as to give each topic its relative associations in the entire subject. This is regarded as of distinct pedagogic importance and in our experience has established its value. It may also serve as the basis of the problem method in the teaching of pathology, but before problems can be set it seems essential to provide a background of major and minor premises in the mind of the student.

Many of the illustrations were made under the direction of Doctor Simon Flexner for a book on pathology which he proposed to write. Manifold duties prevented him from completing a manuscript and the illustrations have been turned over to the author, who cordially acknowledges his gratitude. Thanks are due the Surgeon General of the Army and Major James F. Coupal for the use of photographs made at the Army Medical Museum, Washington, D.C. Other illustrations have been made from a rich material provided by association with several hospitals in this and other cities. The entire list of illustrations has been carefully selected and limited. Their purpose is to clarify the text rather than to provide a pictorial atlas.

It is a pleasure to express grateful appreciation of aid rendered by numerous friends. Maurice L. Richardson, M.D., Benjamin S. Kline, M.D., and Harry Goldblatt, M.D., have given freely of their time in criticism of the manuscript. Miss Catherine E. Lennon, who has prepared the index and repeatedly typed the manuscript, has been an invaluable and faithful assistant. Mr. J. C. Harding, Librarian of the Cleveland Medical Library, has kindly checked the references. The drawings have been made by Mr. Louis Schmidt and Mr. E. F. Faber. Several friends, notably Wade H. Brown, M.D., Louise Pearce, M.D., and Stanley Cobb, M.D., authorities in their fields, have criticised certain parts of the manuscript. The author absolves all of these from responsibility for statements in the text but extends his warmest thanks for their interest and help.

HOWARD T. KARSNER.

CLEVELAND, OHIO.
September 1, 1926.

INTRODUCTION

PATHOLOGY is admittedly one of the fundamental subjects, if not the basic subject, of the medical curriculum. The reasons for this are perhaps obvious, because medicine in the last analysis deals with the consequences of disturbed function or altered structure of the organs and tissues, which induce the symptoms collectively termed disease. Therefore, without an understanding of pathology we can have but an imperfect, and at most empiric, notion of the essential nature of disease.

Moreover, disease itself is not a fixed or static condition; it appears in a great variety of forms and degrees of intensity, of which some progress towards restitution or recovery, and others towards dissolution or death. Hence disease is not a state, but a process ever changing its manifestations, until one or the other terminal stage is reached.

This process includes those modifications arising merely from the aging or senescence of the body in the ordinary course of the development and decline of the individual, as well as the action and reaction of the organs and tissues to many kinds of injurious influences engendered without, and perhaps even within the body. Although parasites are responsible for many disturbances of function and structure, the number and variety of injurious agencies far exceed the limits of parasitic activity and embrace purely physical and chemical effects, to whose action even the injury induced by parasites may come to be ascribed.

The reactive and reparative phenomena, on which restitution and recovery from injury depend, include many general biological or physiological processes, as of growth, immunity, and the like, making the complete exposition of the foundations of pathology a subject so vast as far to exceed the limits of a single volume or manual.

The present volume provides a well considered and successful compromise with regard to the almost endless number of topics demanding inclusion in a textbook on pathology. The work covers the fields of general pathology, pathological or morbid anatomy, pathological histology, functional or pathological physiology, and the general subjects of bacteriology and immunology. Greater detail in the special topics of physiology, parasitology, and immunology may be sought in textbooks devoted particularly to those branches of learning.

The presentation adopted is adequate and proceeds from the general to the particular. The discussion of debated or intricate subjects is sufficient to permit of definite understanding of the points at issue. The subject matter is remarkably complete and the text is lucid; while the illustrations, whether drawings or photographs, are precise and appropriate. In brief, the textbook presents the broad subject of pathology, as now conceived and taught in this country and in Europe, in a manner suitable for the medical and

biological student, as well as for the practitioner of medicine desiring to keep abreast with the ever enlarging subject of pathology. The references to special articles and treatises at the end of the chapters are well chosen, and they contain properly a preponderance of publications in English. The typography, illustrations, and bookmaking reflect credit on the publishers, just as the matter itself is of high credit to the author.

Doctor Karsner has made a notable addition to the English literature on pathology, and the prospective reader is to be congratulated on having available an authoritative and timely manual adapted equally for use as a textbook and a work of reference.

SIMON FLEXNER.

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A TEXT BOOK OF HUMAN PATHOLOGY

CHAPTER I

GENERAL PHENOMENA OF DISEASE

INTRODUCTION.

CAUSES OF DISEASE.

GENERAL CAUSES.

INDIVIDUAL CAUSES.

HEREDITY.

CONSTITUTION AND DISPOSITION.

SPECIAL CAUSES.

DISEASE.

PATHOLOGY.

Introduction.—Health is that state in which the organism is in complete harmony with its environment. Disease includes a variety of conditions leading to a disruption of this harmony, but by common usage excludes congenital anomalies and certain acquired deformities. Disease represents the sum of the action of the cause, and the effects produced by the cause, plus all the retrogressive, progressive, morphological and physiological processes set up in the individual. Pathology is the study of the cause, processes and effects of disease. It therefore concerns itself with the nature of disease. As a matter of practical fact, pathology is concerned with predisposing and exciting causes and with alterations of form and function incident to disease. Essentially, this means the study of etiology, pathological morphology and pathological physiology, the latter including general physiology and biochemistry. It must therefore be assumed that the student has a working knowledge of embryology, normal cytology, histology and anatomy, physiology, biochemistry, bacteriology and protozoölogy. Without this knowledge of the normal, studies of the abnormal rest on an insecure foundation.

Causes of Disease.—The study of the causes of disease is called etiology, and forms an important basis for all work in preventive, diagnostic and curative medicine. Causes may be classified in a variety of ways, such as point of origin within or without the body, and the nature of the agent whether physical, chemical, mechanical, bacterial, or animal, but the most important classes are predisposing and exciting. Predisposing, remote, distant or preparatory causes are those which produce a tendency to acquire disease or prepare the body for the action of the direct cause. Exciting, proximate, determining, immediate or direct causes are those which incite the actual disease processes. Any cause may be classified as general, when it affects large numbers; individual, when it operates on a single organism; or special, when it leads to a special type of disease. Our brief discussion will proceed

on the basis of this last classification including in each group the predisposing and direct action of the factors discussed. A comprehensive discussion is to be found in Roger's book.

General Causes.—These are concerned especially with the environment, such as temperature, air, water, soil, etc. Man, being a warm blooded animal, has a practically constant normal body temperature maintained by the mechanism of thermotaxis, which operates to preserve the level of body temperature in the face of changing environmental temperature. Extremes are better met if the air be relatively dry. High temperatures may, by failure of the body to maintain adequate radiation, directly produce such conditions as heat exhaustion or thermic fever. Dry heat is found by Murphy and his collaborators to increase the number of lymphocytes in the blood, and animals treated by heat are said to exhibit increased resistance to tuberculosis and to transplantable cancers. The local effects of heat are seen in burns of various degrees, varying from mere reddening to acute destruction of tissue. Toxic effects manifest themselves when the burns are extensive, and produce severe lesions of internal viscera. Extremes of heat and cold produce depression of general activity and cold may lead to crowding in ill ventilated places thus increasing exposure to infections. Cold may so reduce circulation in distal parts as to lead to death of those parts or necrosis, which when infected with putrefying bacteria becomes gangrene. Local application of freezing mixtures may have the same effect.

CLIMATIC CONDITIONS deal particularly with heat, cold and humidity, the last emphasizing the effects of the former. Sayres and Harrington find that high temperature reduces capacity for work, but is less effective if the humidity be low. Movement of the air tends to counteract the ill effects of high humidity except when external temperatures are above 37°C . Summer season, for a variety of reasons predisposes to diseases of the intestinal canal, and winter season to diseases of the respiratory tract. It is possible that summer may induce low vasomotor tonus, so that hyperemia of internal viscera ensues. Bacteria flourish on foods in the summer, and introduced into a hyperemic intestinal canal may have a favorable field for establishing infection. Cold, if long continued, may be well borne, but if intermittent so as to produce chilling may lead to hyperemia of internal parts. The investigations of Mudd and his collaborators clearly indicate that such is the case, and if so, local resistance is probably reduced.

It is well known that LIGHT is of importance to the maintenance of health. It is not altogether clear whether these effects are due to long wave lengths, or short wave lengths and it is also probable that simultaneously other influences operate. Brown, Pearce and Van Allen point out the importance of diffuse sunlight as one of the factors which maintain mass relationships of organs and functional activity. We have shown the influence of long wave lengths in combating the poisonous effect of uranium. Numerous investigators, including Chick and her collaborators, Hess and others, have demonstrated the importance of short wave lengths in the prevention and cure

of rickets. It is impossible in the scope of this book to cover a subject so widely investigated and the reader is referred to such articles as those by Sellards, by Bering, by Clark and by Bovie. The special effects of x-ray and radium have assumed great practical importance in view of the use of these agents in therapy. F. C. Wood in his admirable summary of this topic, points out that the Roentgen rays and the gamma rays of radium, of very short wave lengths, can break up the atom. The negatively charged particles, rather than the rays, induce destructive processes in the body cells, primarily by action on the nucleus. Small doses stimulate and larger doses depress mitosis; still larger doses kill the nucleus, without necessarily killing the cytoplasm. Lazarus-Barlow finds that in the testis and intestinal mucosa where mitotic figures are normally frequent, radiation reduces the number of mitotic figures and those found are deformed. During growth and division it is probable that cells are increased in permeability. Packard notes that among other effects of radiation is increased permeability of cells. Therefore degeneration of the radiated cell, or of the dividing radiated cell, is to be expected. In inflammation the activity of fibroblasts is depressed (Maximow). Of the various tissues of the body the bone marrow and lymph nodes are highly susceptible, as are also spleen, sex glands and thymus. The effects on the skin vary from the erythema of moderate duration to destruction of the skin with long standing ulcers, which heal slowly, are resistant to skin grafting and may become cancers (Wolbach). Healed scars are thin, often richly vascularized and are especially susceptible to the rays. If large areas of tissue be destroyed severe toxic effects may result from absorption of poisonous products (see Kolodny, also Doub, Bolliger and Hartman). The effects of radium have also been carefully studied and show some variations from those of x-ray. This matter is well covered in the report on the "medical uses of radium" by the Medical Research Council of Great Britain in 1922. The treatment of tumors by the short wave length rays produces much the same changes in the tumors as in other tissues. The cells show shrinkage and disappearance of nuclei, and the cytoplasm of adjoining cells may fuse to form multinucleated cells. Autolytic ferments dissolve the cells and cell fragments may be taken up and removed by motile large mononuclear cells. The smaller blood vessels become filled with clotted blood and subsequently are converted into scar tissue. The resultant loss of nutrition leads to death of parts of the tumor or other tissue, the dead tissue being removed in part by solution and absorption and in part by the phagocytic cells. The remaining space is filled by proliferation of connective tissue which subsequently condenses to form a scar. The tumor cells are sensitive to the rays and may be killed by doses insufficient to kill the surrounding adult tissues. Certain types of tumor, such as those made up of lymphoid cells, are more sensitive than others. According to Lazarus-Barlow, the changes in tumors following radiation are principally due to strangulation from connective tissue proliferation and starvation from proliferation of endothelium within nutritive blood vessels. Maximow, however, in the study of inflammation finds that radiation has a deleterious influence

on connective tissue growth. Levin and Levine regard the effect of radium upon tumors as due to the destructive effects of the beta rays upon the nearest tumor cells with more remote activity of gamma rays created as secondary to the effects of the beta rays. Murphy, Hussey and their collaborators, as well as Russ and Mottram, have shown that induced immunity to cancer can be reduced by exposure to x-rays, but Wood, Sittenfield and others have not been able to confirm this. Similar exposure reduces the sensitization of the anaphylactic state. It is a general rule that short wave length rays produce deterioration of immune bodies in vitro. Although x-rays are not bactericidal in themselves, Newcomer has shown that they may in the presence of fluorescence, be powerfully bactericidal.

ULTRAVIOLET RAYS have much the same general effects as the milder doses of x-ray and radium. Sunlight, through the action of the ultraviolet rays produces sunburn and in those sensitized by the presence of porphyrins in the body, discussed in the chapter on pigments, may produce more serious lesions. Ultraviolet rays are said to increase metabolism, to stimulate blood forming organs and to increase resistance to infection. These properties account possibly for the beneficial influence of the sunlight treatment of tuberculosis, the ultraviolet treatment of skin tuberculosis (lupus) and other skin lesions, although it is known that ultraviolet rays have also a distinct bactericidal effect.

The influence of photodynamic substances and catalyzing agents cannot be discussed here and the reader is referred to such articles as those of Bering, Clark and the more recent articles of Kinney and of Hauptmann.

Sound is of little importance in pathology except as it may lead to, or increase the intensity of, psychoneuroses. It is said to induce deafness in such occupations as boiler making by producing a chronic fibrosis of the tympanic membrane.

Death may be induced by electric shock, without any important anatomical changes or with only surface burns. Smaller quantities may produce severe burns, due to electrolytic destruction of tissues and cells.

ATMOSPHERE is of importance particularly as concerns pressure, moisture, movements and composition. The optimum pressure for all functions is about fifteen pounds to the square inch. Increases in pressure are well borne for short periods but fatigue appears early. The great danger is of sudden release of pressure, which may produce "caisson disease." Gases are under essentially the same pressure in the body as in the atmosphere, so that sudden release of pressure may produce bubbles in the body fluids and tissues. The bubbles are of greatest importance in the nervous system, where temporary or permanent disease of the tissue may occur. Low atmospheric pressures are observed at high altitudes and especially concern mountain dwellers and aviators. Schneider points out that although high altitudes condition low pressure, decreased temperature and humidity, increased sunshine and electrical alterations, "it is recognized that the controlling element in the physiological reactions is the diminished partial pressure of oxygen and the consequent

imperfect aëration of the arterial blood." The acute symptoms, simulating drunkenness, due to sudden elevation or active exercise before acclimitization, are temporary and easily recovered from. Chronic anoxemia leads to ready fatigue, to an increase in the number of circulating erythrocytes, and although the point is controversial as yet, probably to reduced hydrogen ion concentration of the blood. The moisture of atmosphere is of importance in that increased humidity often leads to ready fatigue and decreased bodily exercise. Humidity also favors bacterial growth. The presence of large bodies of water tends to equalize atmospheric temperatures. The movements of air are of importance in relation to chilling of the body surface and also in blowing insect carriers of disease over wider areas than they could otherwise travel.

THE COMPOSITION OF THE ATMOSPHERE other than as mentioned above concerns particulate content and gases. The particulate content of importance includes bacteria, either in dried form or in minute droplets of sputum or other secretion, protein dusts and inert dusts. Thus, infection may be directly transmitted in the air. Protein particles, such as pollens, epidermis and hairs of animals, may produce asthma, coryza and other reactions in those who are hypersensitive. Inert particles such as carbon, marble, iron, silica are considered in reference to diseases of the lungs in the chapter on pigmentation. The normal gases of the atmosphere may vary in relative amounts and other gases may be present. The latter may be either harmless or directly injurious, as for example carbon monoxide with its production of carbon monoxide hemoglobin, or nitrogen tetroxide (Wood) and other gases such as the war gases, which may directly cause or predispose to pulmonary inflammations. Numerous other lesions may be produced by atmospheric impurities and are important particularly in industrial medicine. Decrease of carbon dioxide is of little significance, but increases are important physiologically (Scott) and may lead to serious pathological disturbances. Oxygen is present in the air in approximately optimum concentration, although wide ranges are possible with preservation of health. Martin, Loevenhart and Bunting find little change until oxygen is reduced to 12 per cent. or less, when important pathological changes occur. We have found experimentally that long exposure to atmospheres containing 80 per cent. or more oxygen induces a pneumonia.

Huntington in an analysis of the geographic distribution of the influenza epidemics of 1918 points to the necessity for further study of how the human subject and the invading organisms are influenced by the atmosphere. Apparently only the weather is of significance in the variations in virulence of the epidemic in different localities.

WATER, as it occurs in atmosphere, has been referred to. Water, as obtained for drinking and washing, as well as its availability for forestation and vegetable growth generally is of the greatest importance in maintenance of health. Its capacity for carrying the exciting causes of certain infectious diseases such as typhoid fever, cholera and dysentery are well known. Sedgwick and MacNutt have observed that in several cities the purification of water has been followed not only by a decrease of water-borne diseases such as typhoid fever

and diarrheas, but also of acute respiratory diseases and pulmonary tuberculosis. The death rate minus the typhoid component is generally decreased. The chemical composition of water may perhaps predispose to disease and there are claims that hard waters may lead to abnormal calcification in the body, but this is not proven. That hard waters produce goiter is probably not true. The work of Marine and Manley indicates that the absence of another chemical constituent, namely, iodine, is probably a most important factor in the development of goiter.

It will be seen that much of the material discussed above deals with hygiene, and for more complete discussion of these subjects as well as the influence of dwelling, crowding, soil, etc., the reader is referred to the texts on hygiene and sanitation.

Individual Causes.—These include age, sex, heredity, constitution, and such personal factors as food, clothing, occupation and psychic influences.

Age may be roughly divided into prenatal life, infancy, childhood, youth, early middle life, middle life and old age. Ballantyne and others discuss conditions of prenatal life, which include such factors as physical condition and nutrition of the mother, disturbances in placenta, fetal membranes and umbilical cord, abnormalities of embryonal and fetal development. At birth the infant is subjected to traumatic influences, to infection during labor and to sudden change in environment. In infancy, food offers important predisposing and direct causes of disease; infections from the immediate family, more particularly the mother, may occur. The infant may possess certain factors of resistance to disease as exemplified in the presence of diphtheria antitoxin. In childhood such protection diminishes, and the child by its more independent life is subjected to changes in temperature, to contact with unclean surfaces and in school life to contacts with numerous sources of infection. In adolescence, sexual development interposes certain nervous factors and the chance of venereal disease. It is a period in which certain infectious diseases such as pulmonary tuberculosis and typhoid fever are likely to occur. In early middle life the individual has business, social and marital contacts which may lead to injurious mental stresses, indulgences of various kinds, exposure to traumatic injuries, and in women to the special stresses of pregnancy, puerperium, care of family, etc. In the later part of this period the incidence of tumors increases, extending through middle life up to the sixtieth year. Old age is complicated by the appearance of atrophic changes in the body and the clinical manifestations of these, as well as of fibrotic changes in blood vessels, heart, kidneys and other organs. Resistance to infections, particularly those of the respiratory tract, decreases. The literature on senility is rich in accurate observations of the condition and in hypotheses concerning their cause and prevention (Metchnikoff, Minot, Child, Pearl).

The most important bearings of sex upon disease refer to the special organs of sex, as for example the tendency for cancer to develop in uterus and in female breast. In addition the sexes differ in their exposure to environ-

mental conditions by virtue of occupation and habits of life. Women are subjected also to the mental and nervous stresses incident to beginning, duration, and cessation of sexual life (menstruation).

Heredity.—This term signifies the genetic relation between successive generations and more particularly the transmission of determinable characters through the germ plasm from one generation to another. It is of importance in pathology and biology generally to distinguish between heredity, congenital faults of development, and intra-uterine acquisition of disease. It is known that certain peculiarities of form are heritable, as for example, webbed fingers and toes and extra digits (polydactylism), cleidocranial dysostosis (McCurdy and Baer) and synostosis (Davenport, Taylor and Nelson). Such may be direct from one generation to the next, or atavistic, skipping one or more generations. Functional defects, such as color blindness may be heritable. To be regarded as a functional defect is the condition called hemophilia, which is transmitted by females but rarely exhibited by them. Morphological characters such as long narrow chest are heritable and may predispose to disease, in this instance to tuberculosis. The disposition to certain diseases appears to be familial and upon a hereditary basis. These include gout, obesity (Davenport), diabetes, asthma, eczema, angioneurotic edema and a number of nervous diseases. Upon what functional or morphological character this rests is not known. An excellent discussion of this topic is presented by Adami.

Disease may sometimes similarly affect several members of the same family. Such familial distribution is not necessarily an indication of heritability but may be due to the similarity of environment, food, habits, etc.

Congenital faults in development include a wide variety of conditions from the simple marking of the body by umbilical cord to the most complex single and double monster formation.

Intra-uterine acquisition of disease, often called congenital disease, is best exemplified by syphilis, in which the fetus becomes diseased due to transfer of the causative organisms from the mother. Other infections can be similarly transferred. Toxic substances the result of disease and introduced poisons, such as chloroform, produce degenerative changes in the fetus similar to those of the mother. Tuberculosis is only rarely of congenital or intra-uterine origin, most of the instances of early tuberculosis being due to postnatal acquirement of the disease. As has been indicated above, immune substances circulating in the maternal blood may also appear in that of the infant. It will be seen that these phenomena are not hereditary in the true sense of the word. Racial susceptibilities and immunities are probably in part hereditary, due to the survival of the fit, and in part congenital; they are discussed fully in the text books of immunology.

Constitution and Disposition.—The medicine of the ancients was so much confused by hypothetical and polemical discussions of constitution, disposition and temperament, that as modern biology with its exact observations developed, these topics apparently lost interest. Nevertheless a recent review

by Hart includes a collection of more than 2000 references, principally in Continental languages. Consideration of the subject in English is reviving, however, as indicated by the work of Draper and others. A tentative but admittedly vague definition is that constitution represents all the morphological and functional characters which control the individual in his relations with his environment, that it is present at birth and is probably hereditary, and that it remains constant in his organism throughout life. Disposition is closely allied in nature but signifies the expression of constitution in the reaction of the individual to stimuli which have the capacity to induce disease. Draper bases constitution upon four "panels," anatomical, physiological, psychological and immunological, all closely interrelated, and offers evidence for the greater frequency of certain diseases in persons of special anatomic form. Graves attempts to correlate between morbidity and scapular form. Child suggests the relationship between susceptibility and rate of oxidative metabolism. Barker offers the hypothesis that anomalies of constitution depend upon the development of certain hormones which arise in the somatoplasm and so change the germ plasm as to account for the variations in the progeny. In general, however, so far as evidence has been adduced it seems wise to regard constitution and disposition as based upon structure and correlated function rather than upon secretions and body fluids, that is, to regard it as fundamentally structural rather than humoral.

Considerable variation of this indefinite aggregation of characters, called constitution, may be present and still be compatible with health, but since the aggregate variation may limit the individual's power of adaptation to the environment, each variant may entail some special predisposition to disease. These individual or personal variants may be roughly classified according to Barker, as morphological variants, exhibited as differences in physical build, functional variants, manifested as differences in biochemical composition, and evolutive and involutive variants, characterized by differences in times of reaching developmental acme or in times of appearance of the phenomena of senescence. For example, a morphological variant consisting of an asthenic habitus is believed to be more susceptible to tuberculosis, and a functional variant who metabolizes or eliminates purines slowly may develop gout.

If the constitution of an individual whose variants are so limited as to be compatible with health may be described as a "status normalis," the various types of constitutional anomalies described become more understandable. The status asthenicus, the status thymolymphaticus, the status hypoplasticus, the status exudativus and the status arthriticus are among them, and such anomalies of constitution are believed to predispose to certain organic and functional diseases.

Such a classification is obviously indefinite and unsatisfactory because in the several anomalies mentioned there is such manifold overlapping. Davenport has catalogued over sixty-nine human variants that are transmitted according to the Mendelian laws. Although this is only a beginning, it represents an attempt at a scientific analysis of the make up of constitution and disposition.

Special Causes.—These comprise those agents which give rise to special forms of disease, and although including physical and chemical agents which bring about special tissue changes and reactions, refer principally to the living causes of disease. These are the bacteria and higher vegetable parasites, the protozoan and metazoan parasites. Thus, typhoid fever is specifically caused by the bacillus typhosus, blastomycosis by a higher vegetable form the blastomyces, malaria by the plasmodium malarie, uncinariasis by the uncinaria. Space limits make it necessary to refer the reader to texts on bacteriology and parasitology for further discussion. Although these organisms are the direct and exciting causes of disease, the presence of one infection may predispose to the acquisition of another, and the survival of infection may leave residual faults of structure and function, which may predispose to subsequent infection of the same or other nature. The general features are discussed in the book by Councilman. Furthermore the various aspects of resistance and immunity are of great importance and are discussed in the text books on this subject.

Disease.—Predisposing causes prepare the way for the direct causes. Direct causes may, and often do, operate without any observable or known predisposing factors. Disease represents the interaction of cause and host. Disease then is the effect resulting from the cause, but is more concretely represented by abnormalities of form and function in the host. Disease may be acute, running a more or less regular or limited course, or chronic with an irregular, indefinite and usually progressive course. The regular course of acute disease may be continuous or periodic. The periodic form may be intermittent, in which there are paroxysms of manifestations with intermissions during which the symptoms disappear although the disease is still present, or it may be remittent, in which the symptoms are continuously present but show remissions during which symptoms are considerably ameliorated. A modification of the intermittent type of disease is the recurrent or relapsing type. Here the patient has a period of symptoms and apparently recovers only to be the victim of another similar attack. That true cure is effected in the interval is not always the case. Disease of this type may gradually become transformed into chronic disease, which is usually continuous, but may show some slight degree of periodicity. Among other classifications must be included that on the basis of severity. Thus, disease may be benign and of little importance to the patient, severe or intense. It may be fulminant or blasting with acute onset, short duration and early death. Malignant disease usually refers to malignant tumors, but is also applied to types of disease with serious symptoms, usually with destruction of tissue and fatal to the patient after a variable course. No consideration of disease can be complete without reference to the defensive mechanisms of the body as exemplified in structure of soft tissues, skin and bones, defensive substances such as immune bodies and ferments in the body fluids, activities of cells particularly the phagocytes and reserve powers in organs to compensate for disease disturbances.

Pathology literally covers all these subjects. In order to conserve space in books on the subject and time in its teaching, it may safely be considered

that detailed treatment of several of the items is adequately presented in texts on hygiene and sanitation, bacteriology, parasitology and immunology. This leaves for more particular consideration the abnormalities of form and function incident to disease. The term lesion refers to such abnormalities as affect special sites; when unqualified it refers to abnormalities of form, otherwise it is spoken of as functional lesion. General pathology treats of disturbances which are common to various tissues and organs of the body such as degenerative and infiltrative processes, pigmentations, calcareous and other mineral deposits, circulatory disturbances, inflammations both non-specific and specific, progressive tissue changes such as hyperplasia and hypertrophy, and tumors. In a rough way these may be classified as retrogressive changes, where the processes are deteriorative, and progressive where multiplication or enlargement of cells is concerned. General pathology defines terms and explains the laws of pathological processes. Special or systemic pathology deals with these changes as they affect special organs or organ systems. This arrangement makes it possible to consider the more prominent effects of disease in a particular organ or system, but in such a mode of study it must not be forgotten that the body is a closely interrelated group of tissues and organs, all operating for the common good, and that disease of one organ or system is not without effects upon the entire economy and is often accompanied by both morphological and functional abnormalities of other organs and systems. Pathology is a division of biology and although the effects may be observed at a given moment, disease is a process rather than a form, exhibits changes from time to time and can therefore be said to have its own natural history and evolutionary phenomena.

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CHAPTER II

PATHOLOGICAL PIGMENTATION

INTRODUCTION.

EXOGENOUS PIGMENTATION.

DUSTS IN THE ATMOSPHERE.

PNEUMOCONIOSIS.

RELATION TO RESPIRATORY DISEASES.

TATTOOING.

ARGYRIA.

PLUMBISM.

ENDOGENOUS PIGMENTATION.

BLOOD PIGMENTS.

HEMOGLOBIN.

HEMOGLOBIN DERIVATIVES.

HEMATIN.

MALARIAL PIGMENT.

HEMOSIDERIN.

HEMATOIDIN.

HEMATOPORPHYRIN.

HEMOFUSCIN.

BROWN ATROPHY.

HEMOCHROMATOSIS.

MELANINS.

MELANOTIC TUMORS.

ADDISON'S DISEASE.

OCHRONOSIS.

LIPOCHROMES.

BILE PIGMENTS.

Introduction.—Various pigments such as chlorophyl and hemoglobin play an important part in the normal physiology of plants and animals. Less important in internal physiology are surface pigments such as the colors of flowers and of the skin and cutaneous appendages of animals. Under pathological conditions such natural pigments may be altered in amount, position, or chemical composition. Furthermore, pigments may be introduced from without, and because of quantity or quality may lead to and play a part in pathological disturbance. *Endogenous pigmentation* indicates natural pigment in increased quantity or in abnormal position, or a deposit of a new type of pigment originating within the body. *Exogenous pigmentation* signifies pigment introduced from without. Excellent discussions of pathological pigmentation are to be found in articles by Hueck and by Oberndorfer.

Exogenous Pigmentation.—Pigments introduced from without enter the body in either particulate or dissolved forms. The particulate matter may be in suspension in the air, or contained in foods or fluids. In any case precipitation is the natural sequence and the point of deposition depends largely upon the mode of introduction. Those introduced in solution may be deposited as the result of alteration of the menstruum, or of simple precipitation, or as the result of chemical change in the substance in question. Under the last named circumstance the substance need not be primarily a pigment but becomes colored as the result of the incidental chemical alteration. Particulate matters gain access principally by way of inspiration in the air and are found primarily

in the lungs and regional lymph nodes. The character of the dusts in the environmental atmosphere determines, therefore, the nature of the pulmonary deposit. The term *pneumoconiosis* signifies the deposit in the lungs of a variety of substances such as coal dust, which produces anthracosis; iron dust, siderosis; marble dust, calcicosis; quartz dust, silicosis; vegetable dusts, phyto-pneumoconiosis and others. Tattooing introduces into the skin, pigments in suspension. In any case the pigments are not only deposited in situ but are transferred to neighboring lymph nodes either by the flow of the lymph or by carriage in phagocytes. Endothelial cells are phagocytic for particulate pigments, ingest them readily and may retain them during a long period of time. Further transmission through the lymphatic apparatus may determine remote deposit of pigment, and if secondary degenerative changes such as are seen in tuberculosis occur at the primary sites of pigmentation or in the lymph nodes, the diseased area may rupture into the blood stream and a wide spread pigmentation result. In this condition the liver and spleen are likely to show more marked pigmentation than other organs. The pigments entering the body in dissolved form include particularly lead and silver. These will be discussed after presenting the data on those which enter in particulate form.

Dusts in the Atmosphere.—The dusts of the atmosphere may be classified as of inanimate origin including metallic and non-metallic substances, and of animate origin including animal or vegetable substances. Most atmospheres contain a mixture of these elements, the proportionate and absolute amounts varying with the character of the environment. Dusts may be classified also according to the injurious effects which follow their prolonged inhalation. Those which produce little or no increased mortality from respiratory disease include coal, shale, slate, iron ore, clay, limestone, plaster of Paris and cement. Those, the inhalation of which is associated with an excessive mortality rate from respiratory diseases, include quartz, quartzite, flint and sandstone. Aside from these variations in constitution, the particles vary in size, shape and concentration in the atmosphere. In most dusts the particles are less than 1 micron in size but may reach 0.4 mm. or more. The larger particles are of little significance because they remain suspended only a short time and if inhaled are not likely to pass the defenses of the upper respiratory tract. The finer the dust particles the greater is the likelihood of their entrance into the lungs. The dust may be in the form of amorphous granules, spicules, crystals or fibers with definite form such as hair, wool, cotton, etc. Landis is of the opinion that there is no evidence to support the belief that wool, hair or similar fibers ever do any damage or accumulate in the lungs in any considerable amounts. Schilling, however, maintains that there is an increased disposition to chronic bronchitis and consequent emphysema. The concentration of dusts in the atmosphere depends upon the environment and is different in the country, city streets, offices, shops, mines, etc. Determinations of the amount of dust in a given volume of air are subject to a large factor of error. Estimations vary between 0.2 gram and 3210 grams per million liters. A fair average for dusty atmospheres is probably in the neighborhood of 60 grams

per million liters. Given an eight hour day, about one million liters of air are respired in a working year; yet a lifetime in such atmospheres results in accumulation in the lungs and peribronchial lymph nodes of much smaller amounts of dust than are found in the total volume of air respired. Hirsch has reported in the lungs of city dwellers 0.19 to 2.72 grams carbon, 0.04 to 0.69 gram silica and 0.02 to 0.45 gram calcium oxide per lung. Klotz reports 1.5 to 5.3 grams carbon per lung in residents of Pittsburgh as compared with 0.145 to 0.405 gram in residents of Ann Arbor. Boer has recovered as much as 8.0 grams carbon from the lung of a chimney sweep. McCrae considered that silica constitutes about 0.73 per cent. of the dry lung tissue, but found in the lungs of miners in the hard rock of South Africa 4.47 per cent. silica, equivalent to about 4.0 grams. Hodenpyl found in the lung of a knife grinder 2.7 grams emery powder and 0.9 gram iron oxide. Thorel found 3.5 grams soapstone in 150 grams of lung of a soapstone worker. Langguth reports finding Fe_2O_3 to the extent of 7.9 per cent. of the dried lung of an iron miner. These represent maximal figures and long exposure may result in the accumulation of much smaller amounts in the lung. Where accurate studies have been made no important changes in the lungs are demonstrable to such injurious dusts as silicates up to four years exposure and up to ten or fifteen years in the case of less injurious dusts. Only 4 to 24 per cent. of inhaled dust gets to the lungs, some reaches the intestinal tract by swallowing and much is expired and expectorated.

Comparison of the quantity of dust as given above to the amount of dust in the atmosphere serves to illustrate the remarkable defensive mechanism of the respiratory tract, for were such a mechanism not operative the amount of dust found in the lung at the end of a long lifetime would be considerably in excess of the figures reported. The lungs of young children are free from such dusts but they are found in adolescence and increase as life advances. It is well known that dwellers in dusty atmospheres show greater degrees of pneumoconiosis than those living in clearer atmospheres, and city dwellers show deeper pigmentation of the lungs than those of the country districts. As a rule, silica is found in the lungs before carbon. In most analyses there is a greater amount of silica in the peribronchial lymph nodes than in the lung itself; but the reverse of this is true of carbon and probably also of calcium. A considerable amount of dust is filtered out of the atmosphere in passage through the nose, and much that gains access to the deeper respiratory tract is ultimately expelled because of the activity of ciliated epithelium and the movement of mucous secretion. That which is deposited beyond the line of ciliated epithelium is taken up by phagocytes. Although Westhues states that these phagocytes are of epithelial origin, the general opinion, as expressed by Haythorn, is that they are wandering endothelial cells.* It has been sug-

*The term endothelial cell is used here in its broadest sense. In the consideration of phagocytosis of pigments no attempt at finer distinction is made. In the lungs these cells probably are derived from the flat cells lining blood and lymph vessels or the flat cells of the reticulum. Here also, as in other situations, they may possibly take origin from large mononuclears of the spleen and lymph nodes, Kupffer cells, monocytes of the circulating blood, or other cells. The matter is more fully discussed in the chapters on inflammation and hematopoietic system.

gested that in the passage of these cells along the peribronchial lymphatic spaces toward the hilus of the lung, the phagocytes may discharge the pigment into the larger bronchioles and the material subsequently be expelled by the action of the cilia, but there is little convincing evidence in support of this. Certainly, the pigment travels along the lymphatic vessels and ultimately becomes deposited in the mediastinal lymph nodes, particularly those at the roots of the lungs. Not all of the material, however, travels this far because pigment is found in the lymphatics of the lungs particularly in those places where the spaces are largest, namely, in the angular spaces between adjacent respiratory units, in the larger lymphatics between lobules, particularly under the pleura, and in the perivascular and peribronchial lymph vessels (see Drinker). The deposit of pigment leads to a slight degree of irritation to which the tissues react in the form of a low grade inflammation producing overgrowth of connective tissue, or fibrosis. It is also possible that the phagocytes may undergo metaplasia to form fibroblasts. This inflammatory change is somewhat more severe in the lungs than in the lymph nodes, and is determined not only by the amount but also by the character of the dust.

Pneumoconiosis.—For practical purposes this term may be taken to include anthracosis, silicosis and siderosis. The pathological alterations are described as affecting anthracosis but the same general principles apply to silicosis and siderosis. Anthracosis is so common among city dwellers that

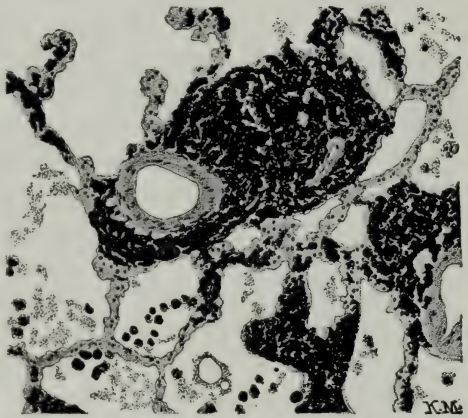


FIG. 1—Anthracosis of lung.

sequential studies can readily be made. Grossly, the lung shows pigmentation under the pleura and in the substance of the lung. In the earlier stages the pleura shows the pigmentation about the apex and the anterior border of the upper lobe and the posterior surface of the upper and lower lobes. Often the lungs show linear depressions corresponding to the position of the ribs, and as a rule these areas are not so deeply pigmented as the convex surfaces between them. In this stage the interlobar surfaces show relatively little pigmentation. As the condition progresses the remainder of the lung surface becomes affected and the pleura exhibits a net work of lines corresponding to the intersections of the septa separating the anatomical lobules. These lines become thicker and more marked and in the most advanced cases the pigment is diffused under the pleura, the intercostal lines showing simply a larger amount of the pigment. Rarely does silicosis or anthracosis reach this advanced stage. In these conditions large masses of material are likely to be deposited at the points of intersection of the lymphatics following the interlobular septa. Here also the lymphatics are likely to be unduly prominent because of a chronic inflamma-

tion. Depending upon the degree of infiltration of dust the lung cuts with ease or interposes a gritty resistance to the knife. In the earlier stages the cut surface shows pigmentation mainly in the lymphatics which accompany the smaller blood vessels and bronchi. With increases in the amount of pigment a network of pigmented lines of interlobular septa may be observed, followed by focal increases where the interlobular lymphatics are large. The latter accumulations may form easily palpable nodules. Finally the cut surface may be diffusely pigmented. The pigmentation as seen in the cut surface does not correspond in the order of distribution to that described on the pleural surface but is spread throughout all the lobes from the beginning. Even in the comparatively early stages the lung may be the site of an overgrowth of connective tissue, more particularly if the material be silica. In the advanced stages, the fibrosis may be severe and is likely to be found about the blood vessels and bronchi and in the interlobular septa. If the deposit be nodular in character fibrosis is particularly prominent in and about the nodules.

Microscopically, the pigment is found in the subpleural lymphatics, particularly where the vessels show their largest calibre, in the lymphatic lakes at the angular junction of alveoli and in the perivascular and peribronchial lymphatics. The pigment in these situations is principally within mononuclear cells whose nuclei frequently are obscured by the mass of pigment. As time goes on these cells may become elongated and appear as spindle cells; but in the ordinary sections cellular outline may not be distinguishable and the pigment appear to be in a fairly solid mass. Carbon is usually in the form of fine granules but it may be found as spicules. Iron is likely to be granular whereas silica is usually in the form of spicules. The individual particles usually measure 1 or 2 micra or less, but measurements as great as 10.5 micra have been recorded. Rarely are pigment granules found free in the alveoli, but it is not uncommon to find occasional mononuclear cells containing pigment within the alveoli, and under experimental conditions these may be found in considerable numbers. Some observers have stated that pigment may be found within the alveolar epithelium, but by differential staining of these cells Haythorn has been unable to confirm this observation. The mediastinal lymph nodes exhibit pigmentation generally parallel in amount to that observed in the lungs but always in more concentrated form. This is usually within mononuclear cells which occupy the sinuses and subsequently obscure and obliterate the follicles. Free pigment is more common in the lymph nodes than in the lungs. Rarely it is possible to demonstrate acute inflammation in pulmonary tissue dependent upon the pigmentation, but as the process advances the formation of connective tissue progresses and is found in and about the situations of greatest pigment deposit. In severe cases the fibrosis may be extremely marked and widely diffused.

Relation of Pneumoconiosis to Respiratory Diseases.—The inhalation of dust may excite catarrh of the respiratory passages. If the dust be organic, as is the case with pollens, effluvia from animals, etc., and the individual be hypersensitive to such proteins, marked coryza and even asthma may develop.

Earthy and metallic dusts may excite mild catarrhs of the upper respiratory passages. The more severe respiratory diseases to be considered in relation to pneumoconiosis include pulmonary tuberculosis and pneumonia. In evaluating the results of studies on the relationship of pneumoconiosis to tuberculosis, it must not be forgotten that the latter disease is caused by the tubercle bacillus and that various conditions in the individual are of great importance in the development of that disease. Carbon has no direct influence upon the growth of the tubercle bacillus. A great factor in the limitation of the tuberculous process is encapsulation by fibrous tissue. As has been indicated, the deposit of dust leads to fibrosis which, in the opinion of Klotz, aids in limiting the tuberculous process. Furthermore, tuberculosis spreads through the lymphatic apparatus and if the pigmentary fibrosis involve lymphatics so as to retard or prevent flow, then likewise must it exert some influence in preventing the dissemination of tuberculosis. Tuberculosis is not more frequent and in fact may be less so among coal miners and chimney sweeps than among other individuals, whereas hard rock miners appear to be more susceptible than others. Pneumonia was found to be more common in the smoky districts of Pittsburgh than in the less smoky areas. Pneumonia is also common among miners, particularly those who work in hard rock and therefore are exposed to silica. Haythorn claims that delayed resolution and organization are common in pneumonia patients who are also victims of anthracosis, and believes that the unfavorable course of the disease is due to the retarding of lymph flow by the fibrosis of the lymphatics.

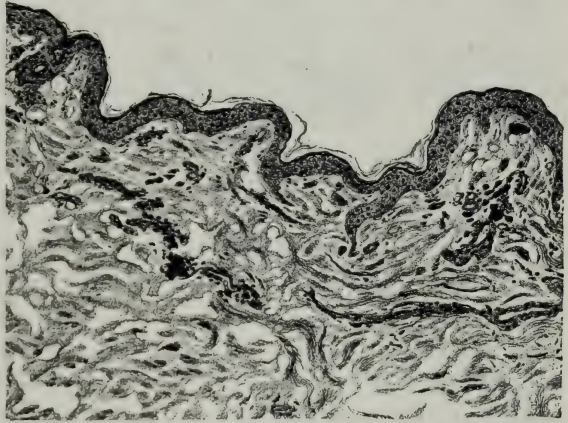


FIG. 2.—Tattooing of skin, showing pigment in upper layers of corium.

The harder dusts, more particularly silica, have a different import. Silicosis may produce serious lesions of the lungs (Legge). Lanza, in a personal communication, points out that workers in the hard rock mines of Montana show atypical pneumonias with delayed resolution, organization, empyema, and subsequent pulmonary tuberculosis. Landis emphasized the importance of hard dusts as directly injurious to lung tissue and predisposing to tuberculosis. Greenberg establishes an extremely high incidence of pulmonary tuberculosis in stone workers and ax polishers and grinders. Kettle believes that silica not only favors tuberculosis by its physical effects but also has some specific effect on the growth of the bacillus.

Tattooing.—As is well known, the art of tattooing is practiced by introducing pigment into the skin by means of a needle. The pigment appears in

the lymphatics of the corium but in the earlier stages it may appear in tissue spaces. There is no doubt that this material is taken up by endothelial cells. Although there must be reaction of connective tissues in response to the

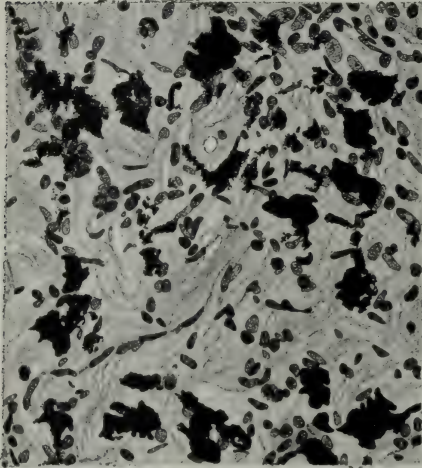


FIG. 3—Tattoo pigment in lymph node.

presence of this foreign body, nevertheless, in the usual sections of the skin from a tattooed individual there appears to be little or no fibrosis that is demonstrable when compared with the other connective tissue of the corium. The pigment granules rarely exceed 1 or 2 micra in size and usually are in the form of small granules. In ordinary sections these granules and spicules are found within endothelial cells which are not easily distinguishable because of the fact that they are overloaded with the pigment granules and crowded together. Transport to the lymph nodes draining the area of tattooing is frequent. Here the pigment is found first in the sinuses

of the lymph nodes, but in those instances where the pigment accumulates in great amounts it may encroach upon the follicles of the nodes.

Argyria.—This form of pigmentation usually occurs as the result of ingestion over a long period of time of silver nitrate or some other drug containing silver. This is an example of exogenous pigmentation following ingestion or absorption in dissolved form. Unless given in excess the drug can be eliminated and no pigmentation occurs. The skin of an individual the victim of argyria is ashen gray. In extreme cases a blue tinge is seen and in the more advanced cases pigmentation of the conjunctiva and of the mucous membranes may be present. The deeper viscera may also be the seat of this pigmentation and in severe cases may show grossly the ashen gray color. Upon microscopic examination it is found that the pigment is deposited between rather than within cells, apparently occupying the cement substance, although Ohmori demonstrates that it is in the membrana propria. Upon fine examination of lightly pigmented blood vessels

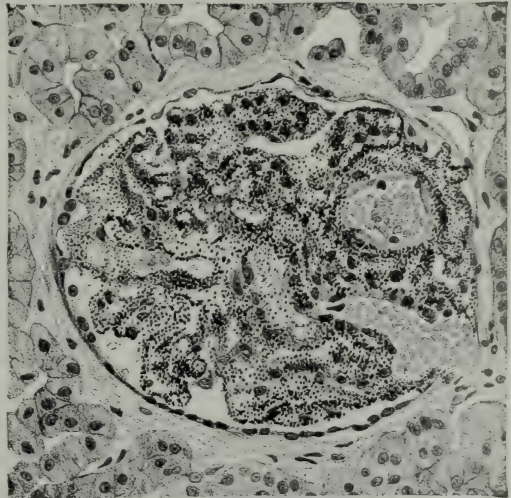


FIG. 4—Argyria of human kidney, showing pigment granules in and about endothelium of glomerular capillaries.

a network may be seen such as is the case in artificial staining with silver salts to demonstrate the outline of endothelial cells. In the skin the pigment is found in the upper layers of the corium immediately under the epithelium and about the sweat and sebaceous glands. In the kidney the pigment is found in the glomerular loops, between and about endothelial cells of these vessels, as well as in the connective tissue immediately surrounding the epithelium of the tubules in the zone at the junction of cortex and pyramid. In the liver, the sinusoids, the smaller branches of the hepatic arterioles and of the portal veins may show the deposit, but it is not found in the glandular structure. In other organs the same relative position of the pigment is found. The pigment is in the form of minute opaque granules. There is no evidence of direct irritation in the form of tissue reaction, nor is there good evidence of serious functional disturbance.

Plumbism.—Lead poisoning is common among those who work with this material. Apart from the symptoms of colic, peripheral paralyses and anemia, victims of this disease frequently show at the line of junction of the teeth and gums a deep blue pigmentation. The lead may be absorbed directly through the skin or enter the body through the nose or mouth in the form of dust either as a soluble or insoluble salt. In either case it circulates with the body fluids in the form of a soluble salt which on coming in contact with the hydrogen sulphide formed about the teeth, as the result of decomposition of food, leads to the formation of lead sulphide; this is deposited about the margin of the gums and produces the "blue line."

Other metals may be deposited in the body but usually this occurs to such a slight extent that visible pigmentation is not observed. The work of Cole and Driver shows that following injection of salts of mercury, globules of metallic mercury may remain at the point of injection. Cases of bismuth poisoning have been reported in which pigmentation appears in the mucous membranes, particularly those of the colon and rectum.

Endogenous Pigmentation.—The human body is provided normally with a variety of pigments which include blood pigments, bile pigments, melanins and lipochromes. The normal blood pigment is hemoglobin, which may be increased in amount in polycythemias and decreased in anemias. As a part of hematopoiesis, the hemoglobin undergoes a series of destructive and reconstructive changes. It is probable that bile pigments are derived entirely from the blood pigment, but bile pigments are so characteristic and under pathological circumstances produce such striking changes that they deserve special and separate consideration. The melanins are found in the pigment of the hair, skin and choroid coat of the eye. The lipochromes give the color to fat, to the corpus luteum of the ovary and appear in other situations.

Blood Pigments.—Hemoglobin is composed of a protein, globin, of basic nature probably allied to the histons, and a pigment presumably acid in nature called hemochromogen or hematin. In spite of the fact that blood destruction and formation are constantly going on, hemoglobin is not normally present, at least not in demonstrable amounts, in the blood plasma or tissue

fluids. Diseases associated with abnormally active blood destruction may be accompanied by the presence of considerable quantities of hemoglobin in the plasma, a condition termed *hemoglobinemia*. The kidney appears to have a fairly definite threshold for excretion of hemoglobin and if the amount in the blood exceed that amount contributed by about one-sixtieth of the total bulk of corpuscles, the pigment appears in the urine, *hemoglobinuria*. Postmortem examinations often show a red stain of the aorta, heart valves and other tissues as the result of destruction of blood corpuscles after death and the consequent liberation of hemoglobin. In all these instances the pigment is in dissolved form and the staining diffuse. Although not easily crystallizable, hemoglobin crystals, orange-yellow and irregularly acicular, may be found in decomposed blood especially after alcohol fixation, but probably never appear in this form during life. Hemoglobin itself is but slightly if at all toxic, and hemoglobinemia and hemoglobinuria probably add little to the seriousness of those diseases in which they appear, malaria, infectious and hemolytic jaundice, paroxysmal hemoglobinuria, hemolysis following transfusion, and other similar conditions.

Hemoglobin in solution in the plasma or within the red blood corpuscles may be transformed to methemoglobin, as seen in poisoning by coal tar derivatives as well as by chlorates and by nitrobenzol. Bacteria may produce methemoglobin in vitro and in vivo, as has been demonstrated with the pneumococcus, streptococcus viridans and other organisms. Nitrites formed in the intestine may be absorbed and produce methemoglobin. Hydrogen sulphide may likewise be absorbed and combine with hemoglobin to form sulphur-methemoglobin which is readily decomposed by weak acids to form methemoglobin. The green discoloration of the belly of cadavers is due in part to the formation of sulphur-methemoglobin. Methemoglobin stains tissues a chocolate-brown as compared with the bright red of hemoglobin staining. The blood and urine likewise exhibit a chocolate-brown color due to the presence of methemoglobin. Its positive identification depends upon spectroscopic examination.

Pigmentation by Hemoglobin Derivatives.—Although the transformations of hemoglobin in normal blood destruction and formation are not clearly understood, Addis furnishes an acceptable working hypothesis. Old erythrocytes are taken up by endothelial phagocytes of the spleen and lymph nodes and by the Kupffer cells of the liver where they are broken down and the hemoglobin liberated (see Jones). The endothelial phagocytes discharge hemoglobin into the plasma and this is taken up by the Kupffer cells from which it passes to the liver cells. Here, the globin and hematin are separated. The molecular constitution of hematin shows four pyrrol nuclei ($\text{CH}, \text{CH}, \text{CH}, \text{CH}, \text{NH}$) linked together and to an atom of iron as well as to other sidechains. The formation of bilirubin in the liver cells is not well understood, but the formula of bilirubin ($\text{C}_{33}\text{H}_{35}\text{N}_4\text{O}_6$) as compared with that of hematin ($\text{C}_{34}\text{H}_{30}\text{O}_4\text{N}_4\text{FeCl}$) shows a loss of iron and an addition of oxygen. Bilirubin is probably isomeric with hematoidin, whose formula, however, is not so well known. There is no

doubt, from the work of Whipple and Hooper and of McNee, that bilirubin may be formed by vascular endothelium and the mesothelium of serous cavities, but normally the liver is the chief even though not the sole seat of this transformation. In the large intestine the bilirubin is reduced to the readily diffusible urobilinogen ($C_{33}H_{43}N_6O_4$), containing a hydrogen atom linked to a carbon atom of one of the pyrrol rings. This is further polymerized in the gut to urobilin which probably contains two molecules of urobilinogen combined under the influence of oxygen. Both are absorbed, but a relatively small amount of urobilinogen appears in the urine. This fact as well as the ready polymerization of urobilinogen into urobilin justifies the assumption that the polymerization takes place in the body and probably in the liver. Urobilin is not stable and is probably polymerized into a substance given the name urobilin-complex, from which it seems likely hemoglobin can be formed. The erythroblast takes up the hemoglobin either as such or in some incomplete form and utilizes it in the construction of red blood corpuscles. It is possible that the liver begins the process of hemoglobin formation and it is then completed in the erythroblast. Whipple indicates that cells other than red cells, including endothelial and others, can elaborate hemoglobin. His scheme of pigment metabolism, authoritative because of his extensive studies of the subject, differs materially from that given above. The central substance is a "pigment complex" which may be derived from hemoglobin, food and body cells and may in turn give rise to hemoglobin, bile pigments, urobilin and urochromogen. He emphasizes the difficulty of establishing a hypothesis which is clearly in accord with established facts.

In pathological pigmentation some of the products of normal pigment metabolism are to be found but others do not seem to occur.

Hematin.—This appears in the body as the result of splitting of the globin of hemoglobin. Except for its appearance in large old blood clots, it is not commonly found. It has been reported in the blood in chromium poisoning, malaria, pernicious anemia and forms of acute toxic hemolysis, congenital hematoporphyrin and in poisoning by certain of the war gases. In particulate form it appears as amorphous, dark brown, almost black granules measuring but a few micra in diameter. Brown, by an extensive series of studies, is convinced that the pigmentation resulting from malaria is hematin rather than melanin as formerly believed.

The pigment of malaria may be found in any part of the body but is particularly prominent in the spleen and liver. The parasite of this disease lives

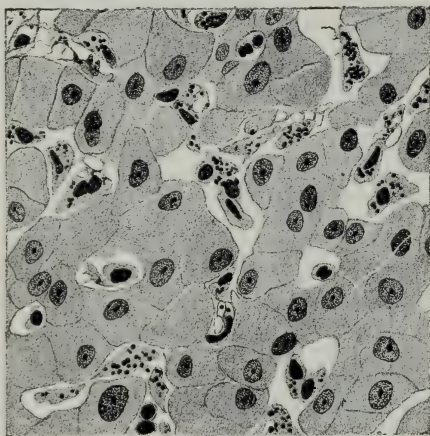


FIG. 5—Malarial pigment in endothelial cells, of liver sinusoids

in or upon the red blood corpuscle and in the course of its development elaborates a pigment, presumably from the hemoglobin of the corpuscle. When the parasite undergoes its asexual division in the human host, it breaks up into several merozoites and the pigment is liberated into the blood. The pigment is taken up by endothelial phagocytes, particularly of the liver and spleen. If sufficiently marked the organs may show grossly a rich brown color. Microscopically the pigment is seen in the endothelial cells of the splenic pulp and occasionally lies free in the tissues. In the liver, it is found in the lining endothelial cells of the sinusoids and in the stellate Kupffer cells. Similar but much less marked pigmentation may be found in the vessels of the brain, intestine and other organs. The pigment is in the form of minute opaque amorphous granules lying within the cytoplasm of the cells. In severe cases of malaria the capillaries of the brain and indeed of other organs may be plugged by parasites containing pigment granules. The pigment contains iron (Meyer), as would be consistent with its identification as hematin, but this iron content was formerly considered to indicate that the pigment is hemosiderin. On account of the difficulty of demonstrating the iron, others have considered the pigment to be a melanin. Schumm, however, has found hematin free in the blood of malaria and Brown has not only demonstrated that the pigment is hematin but states that an alkaline solution of hematin will produce chills and fever in animals, closely resembling those symptoms of malaria. Butterfield and Benedict could not confirm this and maintain that the alkaline menstruum produces slight fever regardless of whether or not hematin is also present. Hematin is further said to be toxic in that it produces glomerular lesions in the kidney and in massive doses produces a fall in blood pressure.

It is generally believed that hematin splits to form hematoidin or hemosiderin, the latter being essentially the same as the former except that it contains iron. Brown argues that inasmuch as malarial hematin remains in the tissues for a long time without change, it is hardly probable that this splitting occurs. If this be true, hematoidin and hemosiderin must be derived from hemoglobin, the final product depending upon environmental conditions.

Hemosiderin.—This pigment is unquestionably a derivative of hemoglobin but except for the fact that it contains iron its composition is not definitely known. This is probably due to the fact that instead of being made up of fixed numbers of elements it exhibits considerable differences in composition. The reason for this assumption is the varying difficulty with which the iron in the pigment may be demonstrated. According to Meyer iron is present in the body in three forms: 1. A firmly bound combination such as hemoglobin in which the iron cannot be demonstrated by staining reactions. 2. Loosely bound combination in which the iron may be demonstrated after forming iron sulphide by the action of ammonium sulphide. 3. Salt-like compounds with proteins in which the iron is readily demonstrable. The iron-bearing pigment of the liver belongs in the second order and is given the name "ferratin." This is usually considered a hemosiderin by most observers but Meyer considers that hemosiderin belongs to those compounds of the third order. Hemo-

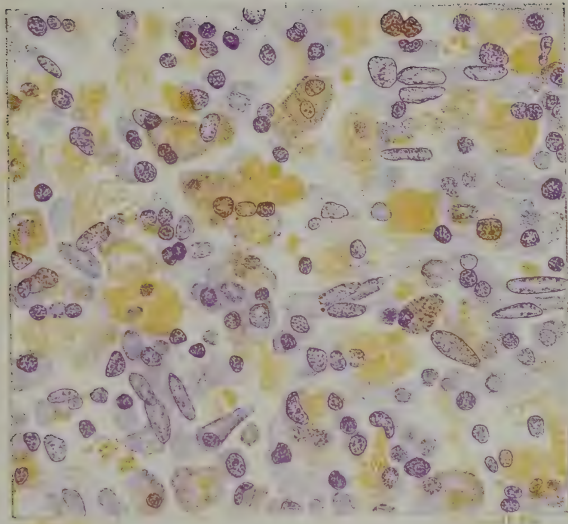


PLATE I—Granules of blood pigment (hemosiderin) in large mononuclear cells (endotheliocytes) around a hemorrhage of the brain.

siderin may be deposited in almost any part of the body as a result of blood destruction. It is observed, however, that for the most part the blood destruction takes place within the cells. Brown is of the opinion that inasmuch as hemosiderin may be formed by autolysis of the liver, intracellular destruction of the blood is not a necessary prerequisite. Nevertheless, the presence of oxygen appears to be necessary, and in the formation of hemosiderin in the liver in autolysis it is probable that an oxydizing enzyme plays a part. The pigment appears as minute golden-brown amorphous granules. In those instances where the iron is very loosely bound it is possible to demonstrate the iron content by the Perl test, or the Prussian blue reaction. The section is immersed in potassium ferrocyanide for ten to twenty minutes, washed in water and left for a few minutes in dilute hydrochloric acid, when the granules are found to show the characteristic blue color. According to Nishimura, ammonium sulphide reacts with more firmly bound iron compounds which are not affected by the simpler test given above. Treatment with ammonium sulphide converts the iron into black iron sulphide. This, however, may subsequently be treated with 2 per cent. potassium ferrocyanide and 1 per cent. hydrochloric acid in equal parts whereupon the Prussian blue reaction takes place.

Although Brown is of the opinion that hematin is not an intermediary product in the formation of hemosiderin and it is not included in the modern theories of metabolism of hemoglobin, nevertheless, it seems probable according to many observers that hemosiderin does play a part in the normal destruction and formation of blood pigment. The iron which is liberated by the destruction of hematin is not eliminated by the body and probably plays some part in the formation of a new hemoglobin molecule.

Hemosiderin is deposited particularly in the spleen and liver, apparently as a part of the normal activity of the body, since this pigment is uniformly present in the liver and spleen of adult man and of many other animals. Pathologically, hemosiderin appears in these two organs and in other organs as the result of excessive blood destruction. This blood destruction occurs in various types of hemolytic anemia, most particularly in primary pernicious anemia. In these diseases the pigment deposit is especially rich in the liver and spleen. Passive hyperemia of various viscera is also an important cause of hemosiderin deposit. It is probable that the stagnation in the capillaries

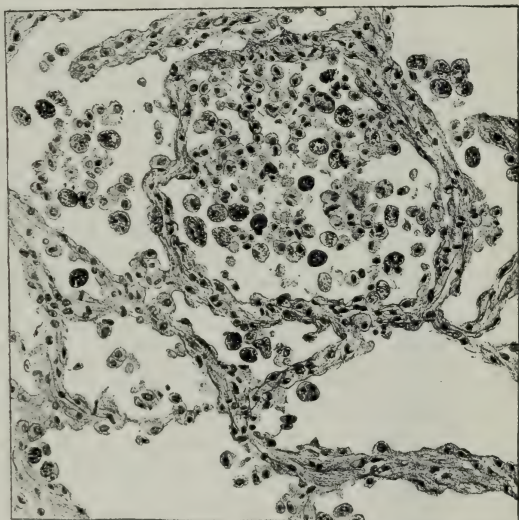


FIG. 6—Hemosiderin in endotheliocytes of the lung.

favors increased rapidity of destruction of the blood. As a result of this destruction the pigment is deposited in those particular parts of the tissue where the hyperemia is most marked. In the liver the pigment is found in the parenchymatous cells. If the condition be simply the result of normal wear and tear of hematopoiesis, only a few of the cells of the central part of the lobule are affected. If the condition be due to passive hyperemia the same general situation of pigment is observed. In case of more extensive destruction of blood, such as occurs in pernicious anemia, all the cells of the lobule may be affected. In advanced cases, hemosiderin may also be found in the endothelial cells of the sinusoids. In the spleen the pigment is found principally in the endothelial cells of the blood sinuses and in similar cells in the splenic pulp, but not infrequently is also found in the splenic pulp outside of cells. Hemo-

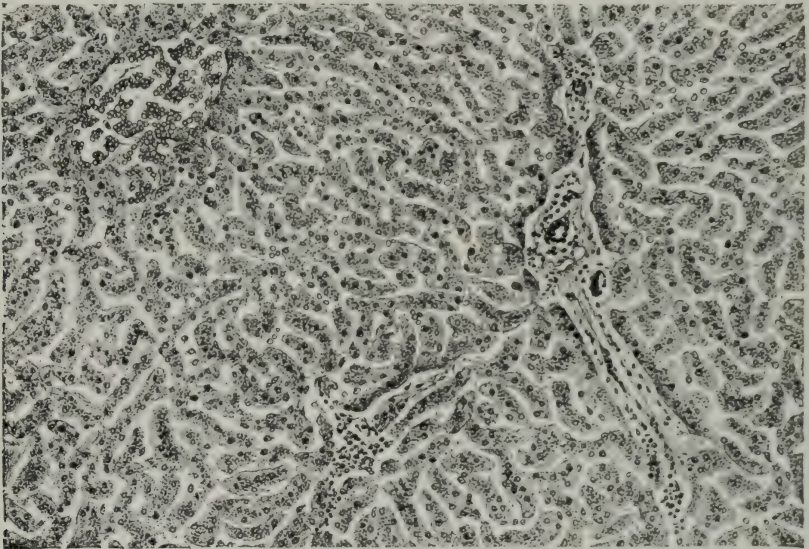


FIG. 7—Hemosiderin in liver cells in pernicious anemia.

siderin pigmentation is sometimes observed in the kidney, more particularly, however, as the result of extensive blood destruction than of passive hyperemia. The pigment may be found in endothelial cells of the kidney, in the interstitial tissue and sometimes in the epithelial cells of the tubules. Occasionally, it may be excreted in the urine where it appears as granules either free or within phagocytic cells. Hemosiderin pigmentation of the lung is found particularly in passive hyperemia of the organ, more especially that due to mitral stenosis. Under these circumstances the pigment is practically entirely intracellular. These cells are probably endothelial cells which take up dead erythrocytes and in the course of time convert the hemoglobin into hemosiderin. The cells are found often in large numbers within the pulmonary alveoli and also in the lymphatic spaces surrounding the bronchioles and blood vessels. Massive deposit of hemosiderin is likely to be found in the same situations in which anthracosis is found. In contradistinction to the "dust cells" which contain

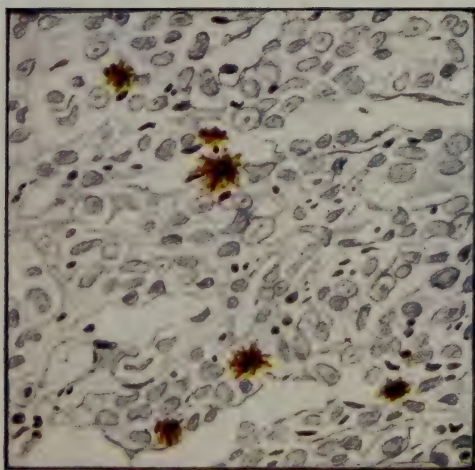
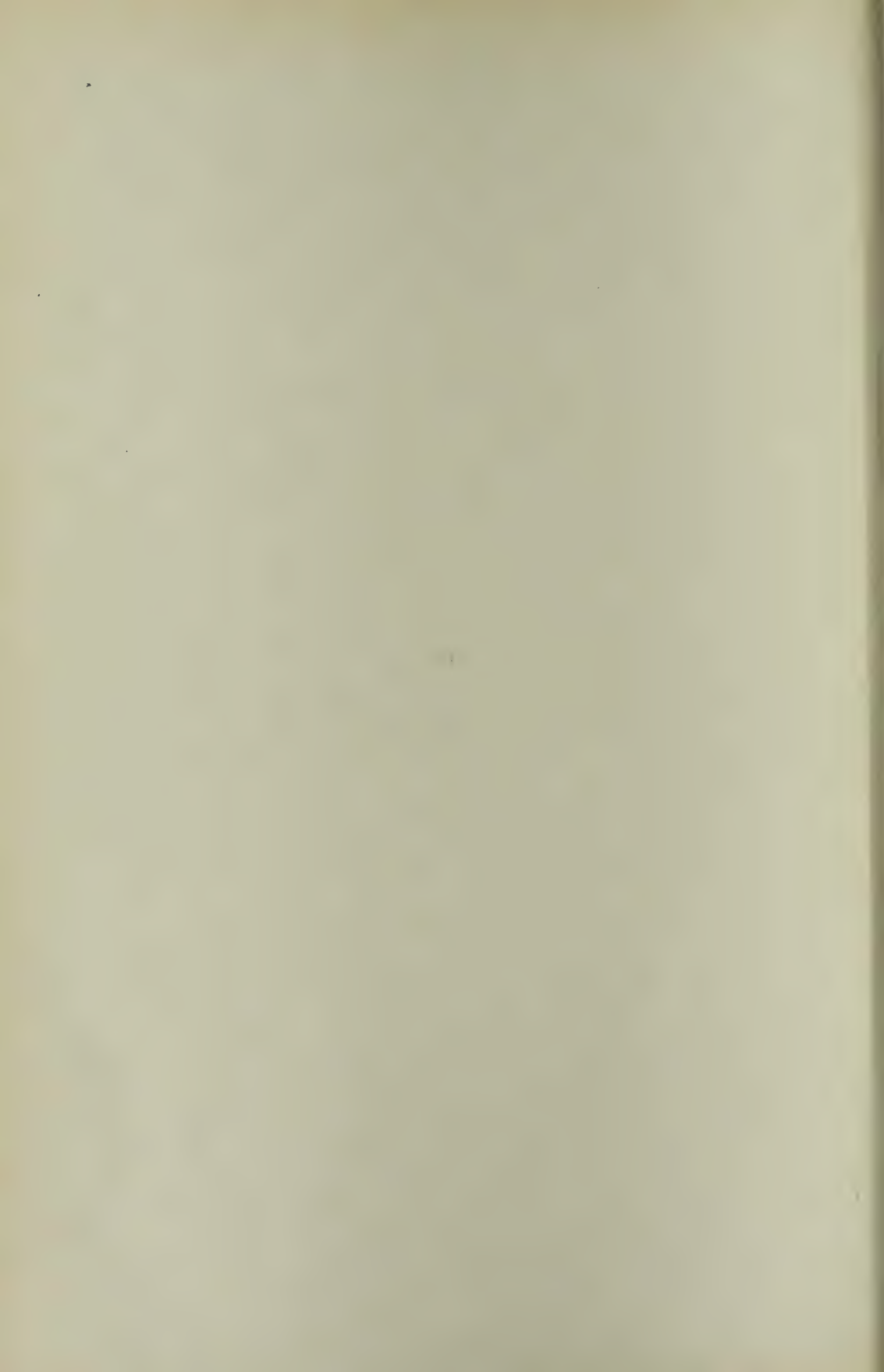


PLATE II—Hematoidin burrs in old infarct of spleen.



inspired pigment, the cells containing hemosiderin are called "heart failure cells." Although fibrosis of the lung appears in connection with this condition, it is probable that the fibrosis depends rather upon the hyperemia than upon the presence of the pigment. In fact, there is little reason for believing that this pigment operates in any situation as an irritative foreign body. In the process of infarction hemorrhage is one of the primary occurrences. The subsequent destruction of the blood leads to hemosiderin formation in the margin of the infarct. This, however, is not likely to be permanent, because the acid formation due to death of tissue leads to solution of the hemosiderin so that it is removed from the part by diffusion. Under ordinary circumstances, however, hemosiderin is relatively insoluble in normal body fluids and when deposited apparently remains in situ permanently. Widespread hemosiderosis occurs in hemochromatosis, to be discussed subsequently. A rare iron-bearing green pigment, principally iron phosphate, is described by Kraus in old infarcts of the spleen.

Hematoidin.—This differs from hemosiderin in that its composition is somewhat more definitely known, and further, in that it is readily crystallized. It is an iron-free product of hemoglobin destruction and is believed to be isomeric with bilirubin. As a pigmentary deposit it is found in places where there

is little or no access of oxygen. It is usually demonstrated readily in old infarcts, particularly those of the spleen. It appears as orange-yellow or orange-red rhombic plates or in the form of acicular crystals bound together so as to form the characteristic "chestnut burrs." It may also be seen in the form of orange-red granules. In the course of generalized blood destruction hematoidin may be formed in large amounts, and when this is the case bilirubin is likely to be formed also in excess. As has been indicated above it is not necessary to presuppose that liver epithelium must act upon the hematoidin, because it is known that bile pigment may be formed otherwise, particularly in serous cavities where hemorrhage has occurred. This is frequently demonstrated in the spinal fluids of individuals who have suffered with cerebral hemorrhage and is not at all uncommon in pleural fluids of those who have hemothorax.

Hematoporphyrin.—This is one of a group of pigments classed under the term porphyrins and related in physiologic activity to chlorophyll. It is

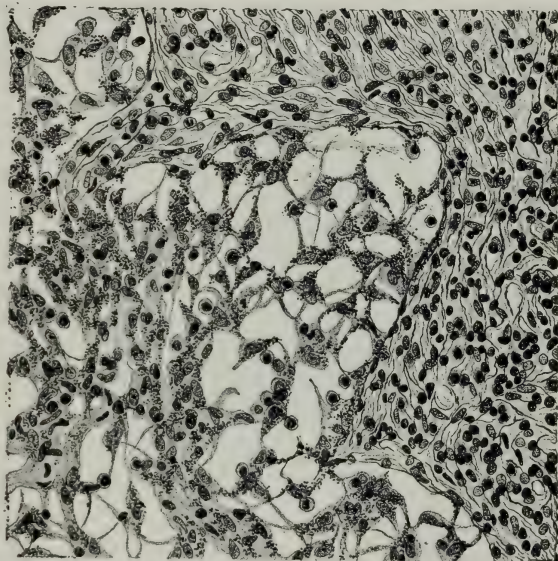


FIG. 8—Hemosiderin in endothelial cells of sinus of retroperitoneal lymph node.

found normally in the urine of man in minute amounts and may be increased in a variety of diseases including rheumatism, tuberculosis, certain liver diseases, as well as after the use of the coal tar drugs sulphonal, veronal and trional. If the pigment be present in large amounts the urine is a Burgundy red in color. In congenital hematoporphyrinuria, an uncommon disease, large amounts of the pigment are found in the urine; in the blood it is accompanied by the presence of free hematin and bilirubin. The pigment can be produced by chemical treatment of hematin. A special predisposition seems to be a factor of importance in the cause of the disease (Harbitz, see also Gunther). Congenital hematoporphyrinuria, as well as certain cases of the acquired form, exhibits a hypersensitiveness of the skin to light. Experimental injections of porphyrins produce extreme sensitiveness of the skin to light with the production of skin eruptions, and large doses given animals may be sufficient to render them victims of "light stroke" after a few minutes exposure to a strong light.

Hemofuscin.—Not infrequently a brownish-yellow amorphous granular pigment is found in smooth muscle cells, particularly those of the intestine. It does not react to the tests for iron, is soluble in alkalis and in H_2O_2 , but is not soluble in dilute acids or fat solvents. Von Recklinghausen who described this pigment believed it is to be derived from hemosiderin, a view generally held to-day, although some regard it as a melanin.

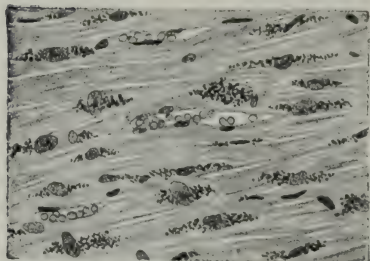


FIG. 9.—Brown atrophy of heart.

Brown atrophy of the heart is considered here because in the past the pigment of heart muscle has been regarded, among other things, as hemofuscin. Dolley and Guthrie point out that the pigments of heart muscle are melanin, and lipochromes of the carotinoid group ingested in the food. The former is the pigment proper of brown atrophy of the heart and the latter varies under normal and diseased conditions. Pigment is present in the child's heart in only small quantities and increases as age advances, the lipochrome varying, however, with disease and probably with the content of carotin-xanthophyll in the diet. Atrophy of the heart may occur without excessive pigmentation, probably because the age and conditions of atrophy are such that pigment is in only moderate amounts. In brown atrophy, the organ is reduced in size and weight, the muscle deep brown in color, and the coronary vessels tortuous because they occupy a shorter space than normal. Microscopically, the muscle fibers are reduced in diameter and length, the nuclei are increased in number and closely approximated (Karsner, Saphir and Todd) and between their poles stretch bands of golden yellow and brown pigment granules. It has been thought that the reduction in volume of the muscle without reduction of pigment is responsible for the deeper color of brown atrophy, but it is probable that there is an absolute increase of pigment, especially if not solely melanin.

Hemochromatosis.—In this condition there is pigmentation of various tissues, and an associated fibrosis. Sprunt found that diabetes accompanied fifty of the sixty-three cases collected. The pigment is deposited in the form of amorphous golden-brown granules in the parenchymatous cells and in the connective tissues. The liver shows a marked overgrowth of the connective tissue of the portal spaces and the organ is usually the seat of an atrophic cirrhosis. In the more advanced cases the pigment is found in greater amounts in the connective tissue than in the parenchyma. The pancreas shows a similar overgrowth of the interlobar and interacinar connective tissue with a rich deposit of the pigment. The spleen and lymph nodes are also fibrosed and pigmented. Grossly, the organs are of deep brown color and exhibit the fibrosis. The skin is bronzed. When associated with diabetes the complex has long been called bronzed diabetes. The amount of iron in the pigmented organs is

enormously increased. Normally, the whole body contains about 3 grams of iron but as much as 38 grams have been found in the liver alone of a case of hemochromatosis. It is probable that this accumulation is due to fault in the elimination of iron in the normal rate of blood destruction rather than to excessive breaking down, although the experimental production of the condition in rabbits, by Rous and Oliver, was based upon hemolysis. Rous and his collaborators found that the pigment is hemosiderin, except for the occasional presence of hematoporphyrin. Von

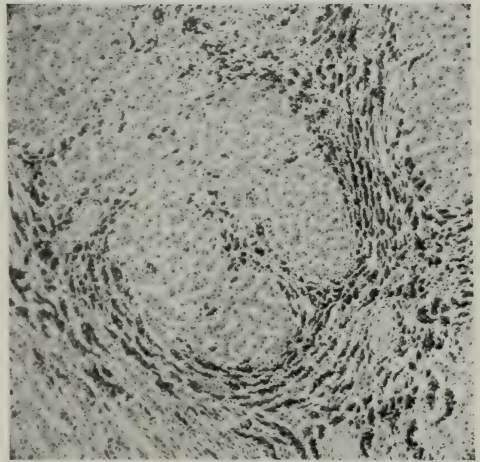


FIG. 10—Hemochromatosis of liver.

Recklinghausen held that the pigments are hemosiderin and hemofuscin, a view supported by Opie and demonstrated by Mallory, Parker and Nye. Rous and Oliver regarded the pigmentation as primary, followed by fibrosis. Whether or not the fibrosis induces further accession of the disturbance of pigment metabolism is not determined. Opie expressed the view that the pigmentation causes cellular degeneration and this is followed by fibrosis. Mallory, Parker and Nye regard the fibrosis as primarily a stroma for regeneration of cells in response to necrosis, with subsequent coalescence of fibrous tissue as the pigmented cells die off. They regard the hemofuscin as the product of the action of a poisonous substance upon hemoglobin set free by normal disintegration of erythrocytes. Most cells, such as endothelial, hepatic and pancreatic cells, transform the hemofuscin into hemosiderin, but others such as duct epithelium, muscle cells, fibroblasts in certain locations, have no such effect and the hemofuscin persists. There is little doubt that some intoxication is basic in the disease, and alcohol has long been suspected as of outstanding importance (Wells). Mallory and his collaborators pro-

duced the disease by the injection of copper salts, found copper in certain alcoholic beverages, and believe that the copper is responsible rather than the alcohol.

Melanins.—These pigments are the product of certain specialized cells found normally in the skin and hair follicles, choroid coat of the eye, pia mater, especially at the base of the brain, and perhaps can be elaborated by certain other cells as those of heart muscle. These pigments have been classified as metabolic, indicating that they are produced by the metabolic activity of the cells, operating probably upon the proteins. Isolated melanins absorb the short rays of the spectrum and in life probably serve to protect against harmful effects of light. Exposure to strong light increases the melanin of the skin as observed in sunburn and freckles. Dark skins are more resistant to chemical irritants than light skins, as shown by Hanzlik and Tarr, and this resistance may play a part in the low incidence of skin cancers in the dark races. Kinney, however, maintains that pigmentation does not prevent penetration of light to the underlying tissue. Most melanins contain nitrogen, hydrogen and carbon and sometimes iron. The presence of iron was considered as evidence that melanins are of hematogenous origin, but the fact that the hematoxyrin ring is absent suggests some other origin. It was formerly thought that sulphur is commonly present, but with more exact methods Brahn finds that it is usually absent and also finds the nitrogen in smaller quantities than in earlier analyses. The larger figures for nitrogen and sulphur were probably due to incomplete purification. Treatment with hemin produces a pigment spectroscopically like bilirubin. Melanins contain the pyrocatechin ring and have some relation to the group of hematogenous pigments. Nevertheless, there is much evidence in favor of the view that some if not many melanins are derived from proteins. When proteins are heated with strong acids a dark colored melanin-like substance is produced and it is known that the aromatic products of protein decomposition such as tyrosine, phenylalanine and tryptophane may produce dark colored substances by the elimination of water and absorption of oxygen. Careful studies of pigment metabolism indicate that an enzyme is of particular importance, and comparative as well as direct studies indicate that this is an oxidizing enzyme. The ink sac of the squid contains such enzymes and the cells of the skin important in melanin formation have a definite oxidizing capacity. Lignac maintains, however, that no ferments are involved. Neuberg found that extracts of a melanoma could produce melanin from epinephrin, and Bloch found that the pigment cells of the skin operate in the same way on substances closely related chemically to epinephrin. According to Wells "von Fürth urges strongly the view that both normal and pathological melanin formation depend upon the action of the tyrosinase or allied enzymes in conjunction with autolytic enzymes; the latter split free the chromogen groups of the protein molecule, which are then oxidized by the tyrosinase, undergo condensation, and take up sulphur- and iron-holding groups and also other organic compounds, the entire complex forming the melanin."

Melanotic Tumors.—Quite aside from tumor growth, the skin and hair may, in the presence of disease, show either increase or decrease in melanin content. Pathological pigmentation may be observed in such faults of development as the pigmented mole of the skin, which are only potentially tumors. True pigmented tumors originate from any position where pigment producing cells exist, in moles, in skin, in choroid coat of the eye, and in pia mater. Rarely such tumors originate in the adrenal and the origin of the pigment is obscure unless the epinephrin have some effect. Pigmented tumors of the rectum probably originate in the skin of the anus. Pigmented tumors are usually called melanoma but the term melanocytoblastoma is probably more correct (Omodei-Zorini). Such tumors are usually highly malignant. In many cases they are obviously connective tissue in origin and are classified as sarcoma. The exact nature of the cells of the pigmented mole is still obscure, and it is therefore difficult to state whether the malignant tumors arising therefrom are sarcomas of connective tissue origin or carcinomas of epithelial origin. The pigmented choroid tumor is extremely malignant, and secondary foci, or metastases, develop very early. These metastases are most frequent and attain largest size in the liver. They are composed usually of spindle cells with rich cytoplasm, irregularly arranged and with a rich vascular supply, the vessels appearing as mere slits in the tissue of the tumor. The pigment is in the form of dark orange amorphous granules in the cytoplasm of the cells. Not infrequently the pigment is present in such large amounts as to obscure the nuclei of the containing cells and it may also appear in extracellular positions. Not all the cells are equally pigmented and in spite of the fact that all cells of the tumor originate from cells potentially capable of producing pigment, many of the tumor cells are free from pigment. Pigmented moles and melanotic tumors in general are discussed in the section on tumors. It is of importance at this point, however, to indicate the extensive disturbance of pigment metabolism seen in cases of extensive melanotic sarcoma. Many of the cases exhibit melanuria. The urine when passed is of practically normal color, but on standing or on addition of oxidizing agents it becomes deep brown or brownish-black in color. The urine may be black when passed, owing

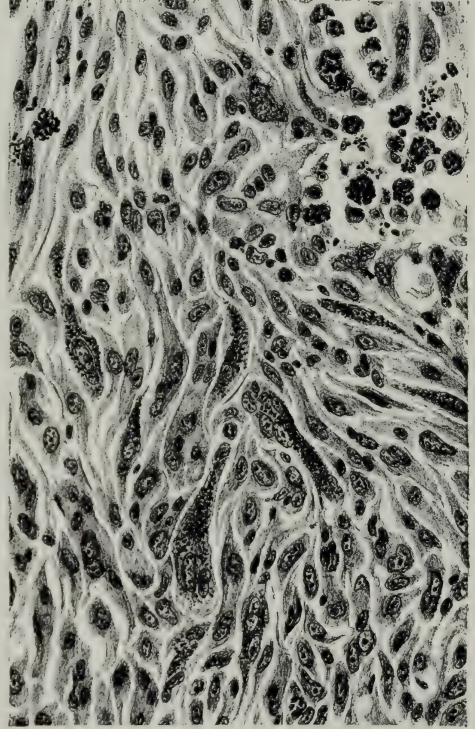


FIG. 11—Melanotic spindle cell sarcoma of liver. Pigment appears in fine granules in tumor cells and in coarser granules in phagocytic endothelial cells.

to the presence in the body of oxidizing substances. The same phenomenon is exhibited following subcutaneous injection of melanin in rabbits and guinea pigs. It is assumed that in the circulating fluids melanin is reduced, particularly in the liver, to a colorless precursor melanogen, which may subsequently be oxidized to form melanin. The melanin may be deposited in the body in places other than the tumor, for example in vascular endothelium, in lymph nodes and rarely in the skin.

Addison's Disease.—This is a syndrome in which there occur pigmentation of the skin, loss of flesh and strength, rapid and weak cardiac action and low blood pressure, occasionally complicated by vomiting, nausea and other symptoms (Rowntree). The pigmentation of the skin is probably an increase in the amount of the normal pigment of that tissue. It may appear in patches distributed irregularly and without regard to those parts exposed to sun and light, or it may be distributed diffusely over the body. It not uncommonly affects the mucous membranes of the mouth and in the negro this is often the only point at which the pigmentation can be demonstrated. Many of the cases at autopsy show disease of the adrenal, particularly tuberculosis, although other conditions such as tumor and amyloid disease may give a comparable destruction of the adrenal tissue. Many cases of extensive destruction of the adrenal by tuberculosis and other diseases are seen, however, in which Addison's syndrome does not appear. Furthermore, cases of typical Addison's disease are found in which no gross lesion of the adrenal is present. According to more recent investigations it appears that the disease is one of the so-called chromaffin system rather than simply of the adrenals. As is well known, the chromaffin cells, which have a particular affinity for chrome salts, are found not only in the adrenal medulla but also in the retroperitoneal ganglia. Certain cases have been described in which, although there was no material destruction of the adrenal body, yet practically all the retroperitoneal ganglionic tissue had been destroyed by disease. In those cases of destruction of the adrenal without the appearance of the symptoms of Addison's disease, it seems probable that a sufficient amount of chromaffin tissue remains in the retroperitoneal ganglia and in other situations to fulfill the normal function in the body. As far as is known now from the study of the function of the adrenal gland, it appears that the chief disturbance immediately following the destruction or removal of this organ is absence of epinephrin from the blood. In spite of the fact that certain tumors have been described which can oxidize epinephrin with the production of melanotic pigment, this can have no very direct bearing on those cases in which epinephrin is absent or much reduced in amount. It is possible, however, that some of the precursors of epinephrin may remain in circulation instead of being utilized in building up epinephrin. Human skin contains a ferment which can produce pigment by operation upon the epinephrin. If this be true, it is conceivable that such a ferment may act even more powerfully upon some precursor of epinephrin with the same general results. Inasmuch as the skin pigment of Addison's disease has not been analyzed exactly, it is impossible to say that it is positively the same as that which

appears normally in the skin. Certainly the adrenals play some part in pigment metabolism since Königstein has shown that if animals be subjected to adrenalectomy or be given repeated injections of epinephrin, they may show an increased amount of pigmentation. Bloch offers the hypothesis that cells of the skin may oxidize a precursor of epinephrin, 3,4 dioxypyphenylalanine, into melanin. In severe cases the presence of melanin similar to that seen in melanuria of melanotic sarcoma is found in Addison's disease, and in other instances crystals resembling hematoidin have been found in the pigmented parts. Grossly, the pigmented skin and mucous membrane are of a bronze color resembling that seen after long exposure to the sun, but in this instance not limited to the exposed parts. Microscopically, the pigment is found in the malpighian cells of the epidermis, and in severe cases may be found in the upper layer of the corium in what are believed to be chromatophore cells. There is no indication that the deposit of this pigment leads to reaction on the part of the tissue. The regional lymph nodes and the deeper tissues of the body do not show pigmentation.

Ochronosis.—This rather rare condition exhibits pigmentation of cartilages, joint capsules, tendons, sometimes of the intima of blood vessels and of the epithelium of the kidney (Oppenheimer and Kline). There are usually no other symptoms and the patient's only complaint is the blue color of nose, ears and other places where the pigmented cartilage is seen through the skin. The name was given by Virchow because of the ochre color of the cartilages in the condition as he reported it. In some of the cases alkaptonuria appears, a condition in which the urine turns dark on exposure to air owing to the presence of homogentisic acid. In the earlier stages of the disease the pigmentation is diffuse but subsequently is found in the form of minute amorphous iron-free granules. The cause of the disease is unknown, but in one-fourth of the cases reported by Poulsen there was a history of prolonged dressing of wounds with phenol, producing the so-called exogenous ochronosis. Virchow believed the pigment to be a hematin derivative but Hansemann and Pick and others conclude that it is a melanin. According to Pick the pigment is formed from the influence of tyrosinase upon the aromatic groups of the protein molecule such as tyrosine and phenylalanine and related hydroxylized products. Similarly, the action of a like ferment upon absorbed phenol leads to the same condition. Following a purely endogenous or exogenous origin homogentisic acid may be produced from the aromatic groups and appear in the urine. Alkaptonuria is not a necessary part of ochronosis, occurring in about half the cases, but may appear independently of ochronosis.

Malarial Pigmentation.—Many authorities consider that the pigment of malaria is a melanin, but Brown, in agreement with Carbone, considers it hematin or an immediate derivative since it contains iron and has the same solubilities and spectroscopic properties as hematin. Ewing also finds that malarial pigment behaves toward solvents as do the blood pigments. He is of the opinion, however, that there are several pigments found including that elaborated by the parasites as well as hematoidin and bilirubin or urobilin

crystals or granules. In agreement with Brown, malarial pigment has been discussed with blood pigments.

Lipochromes.—These are pigments found in fat, corpus luteum, epithelium of seminal vesicles, epididymis, testes, in ganglion cells and in the Kupffer cells of the liver. They are of yellow color, are soluble in fat solvents and probably contain both neutral fats and cholesterol. They stain with the fat stains scarlet R and Sudan III and occasionally with osmic acid, this last variant probably depending on the content of oleic fats. It has been shown that most if not all the lipochromes, which include the carotinoid pigments, xanthophylls, anthocyanin and flavon flower pigments, are exogenous and introduced through the diet. Escher found that the pigment of corpus luteum is identical with plant carotin. Palmer has demonstrated that withholding

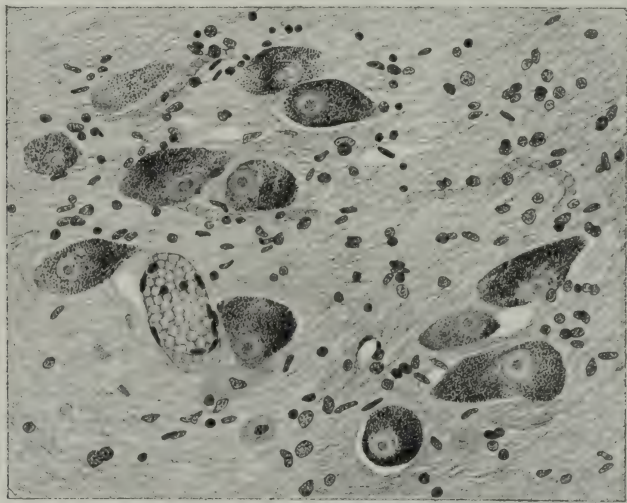


FIG. 12—Pigmented ganglion cells.

the plant pigments from the diet leads to an absence of pigments from fat, egg yolk and blood serum of animals, in spite of which the animals are healthy and the eggs fertile. He states that carotin contributes the pigment of the fat and corpus luteum of the cow and that xanthophyll colors the egg yolk, body fat and blood serum of the fowl. Dolley and Guthrie have demonstrated that the pigment of ganglion cells is carotin. Dolley's work on brown atrophy of the heart has been referred to. It is possible that in man certain fat pigments are not of this group and Currie states that "adipochrome" of human fat does not react chemically as do the plant pigments. The so-called lipofuscins, which are said to take fat stains but otherwise behave differently from lipochromes, are regarded by Hueck as "waste pigments." Lubarsch, however, would include these as grouped with melanins and states that while not fatty they may have such affinity for lipoids as to produce the fat reaction.

The carotin-xanthophyll pigments may be ingested in such excess as to color skin, blood plasma and urine (Head and Johnson) and the same may be

true of anthocyanin (Ruh and Garvin). Chloroma, a rare tumor of myelogenous origin, has a yellowish-green color. Although Ottenberg expressed the belief that some of these tumors are colored by a rich content of eosinophiles, yet many tumors of this sort contain few or no eosinophiles and contain a fat-like pigment in refractile globules, which usually stains with osmic acid.

Xanthoma is an uncommon condition in which there are single or multiple flat tumors of the skin or of other parts, exhibiting an orange-yellow color due to the fact that the cells contain and apparently elaborate an orange-yellow lipochrome probably of the nature of a myelin or a cholesterol fatty acid ester. This condition sometimes complicates diabetes, xanthoma diabeticorum, in which case the blood may be unusually rich in cholesterol, indicating a serious disturbance of lipid metabolism. Disturbances of fat metabolism are not rare in diabetes, as indicated by the terminal fixed acid acidosis. The latter condition may possibly be a precursor or play a part in the change in lipid metabolism, and together the two may be important in the development of the xanthoma. Xanthoma tuberosum multiplex is similar except that there is no diabetes, no pain or tenderness of the lesion and no inflammatory areola. Tumors of various kinds may contain xanthoma cells and they occur in other conditions, such as xanthelasma. This lesion appears in the corium of the skin, the epidermis being elevated in the form of papules three or four millimeters in diameter and of deep lemon-yellow color. Microscopically, the corium shows a fairly well circumscribed collection of mononuclear cells with a large amount of cytoplasm, containing in the stained preparation many minute vacuoles occupied by the lipid material.

Bile Pigmentation.—The principle pigment of human bile is bilirubin which is probably isomeric with hematoidin. This is oxidized to the green pigment biliverdin, a process which in animals is much more pronounced and common than in man. Animal bile is often green whereas normal human bile shows the brownish-yellow color of bilirubin. Examination of bile stones indicates that other pigments are present but these are probably the product of changes in bilirubin after having been deposited to form the calculi. Although it is undoubtedly true, as has been shown by Whipple and his collaborators as well as others, that bile pigment may be formed in places other than the liver, nevertheless the liver is the most important seat of formation of bile pigment. Pathologically the body may be pigmented by bile either as the result of obstruction to the outflow of bile or as the result of excessive formation of bile pigment with insufficient excretion. In local areas bile pigment may be formed as the result of hemorrhage and therefore may pigment the surrounding tissues. Obstructive jaundice or obstructive icterus is due to occlusion of either the main bile duct or many of the smaller tributaries. Obstruction to the common duct is most commonly due to catarrhal inflammation of the lining but may also be due to the lodgment of gall stones, the contraction of cicatricial tissue, the pressure of tumors or enlarged lymph nodes, actual involvement by tumor growth and various forms of acute or chronic inflammation of the biliary passages. Sometimes inflammation may be of such a nature as not to compress the larger bile

duct but may serve to occlude smaller bile passages. The involvement of the liver by tumors, rather primary than secondary, may also be so extensive as to produce jaundice. Obstruction to finer passages may be seen in chronic inflammatory processes in the liver itself, for example, in hypertrophic cirrhosis of the liver where there is an overgrowth of connective tissue between the liver cords. In the late stages of atrophic cirrhosis the same phenomenon may occur. Jaundice as the result of excessive formation of bilirubin is usually due to great destruction of blood with much liberation of hematin. It is assumed in these circumstances that bilirubin is formed in such great excess that it cannot be excreted by the liver. It, therefore, accumulates in the blood and serves to pigment the tissues. Nevertheless, numerous observations have shown that not only is there an increase in bilirubin formation in these cases, but certain of them also show obstruction to the finer bile canals, not only those between the liver cells but also the very finest canals existing within the cytoplasm of the liver cells. Such obstruction may be due to swelling of the liver cells, or of the cells which line the bile capillaries and to plugging of the biliary passages by fibrin thrombi. It is now considered that the liver is an important seat of fibrinogen formation, and it seems possible that pathological disturbances in this situation may lead to formation of small fibrin plugs. It has also been suggested that the poison which produces hemolysis may also serve to precipitate bile and that the small masses of bile precipitate may serve to plug finer vessels. Local formation of bile pigment may be seen in connection with bruises where not infrequently a greenish-yellow discoloration is observed. Hemorrhage into serous cavities such as the pleura and the meninges may, after a time, lead to the formation of bile pigment. In these situations hematin and other blood pigments are likely also to be present.

Pigmentation by bile is usually in the form of a diffuse coloration of cells and the pigment may be present in various secretions. It is seen externally in the skin and mucous membranes, particularly the conjunctiva. All the deep tissues may be pigmented including connective tissue and intercellular substance. After the bile in the blood reaches a certain concentration it also appears in the urine, and in extreme cases in the sputum and even other secretions. The pigment of the skin and conjunctiva is of deep brownish-yellow color and the same is true of the urine, but in the latter instance exposure to air may lead to sufficient oxidization to transform the bilirubin to biliverdin and change the color from brownish-yellow to deep green. Examination of the blood shows that the plasma is also pigmented, and this phenomenon appears before pigmentation is observed in the skin or secretions. The concentration of pigment in the blood must reach about 1:50,000 before pigmentation of the urine appears. This concentration then constitutes the renal threshold value for bile pigment. Nevertheless, Blankenhorn is of the opinion that cases exist in which the pigment may appear in the skin and not in the urine, presumably because the bile is perhaps in some colloidal combination with protein so that it may be diffused into the skin but not be excreted through the kidney. The bodies of those recently dead suffering from jaundice show a brownish-yellow

pigmentation of the skin, the mucous membranes, the fat, surfaces such as those of the heart valves and aorta, kidney and other viscera. After these organs have been exposed to the air for some time the color changes to a deep green. In practically all cases the pigmentation is deepest in the liver itself. In the majority of acute cases, histological examination of the tissues shows little of the pigment except in the case of kidney disease when casts in the renal tubules may show the brown or green pigmentation. Usually the process of fixation, embedding and staining serves to oxidize the bilirubin so that it appears as the green biliverdin rather than the brownish-yellow bilirubin. In cases of obstructive jaundice that have been somewhat prolonged, the picture in the liver may be characteristic. Under these circumstances precipitated bile pigment may be found in the form of amorphous masses in the bile ducts and in the bile capillaries. In the finer division of the bile capillaries the pigment may be found in irregularly stellate forms, due to the fact that the mass in the bile capillary is connected with that deposited in the intracellular biliary canaliculi. In the course of preparation of the tissue the mass of bile pigment frequently shrinks, as do also the cells, and there is likely to be a small areola around the pigment between it and the surrounding cells. As has been mentioned above, in certain cases of jaundice due to destruction of blood there may be found small fibrin clots and marked cloudy swelling of the parenchymatous cells of the liver.

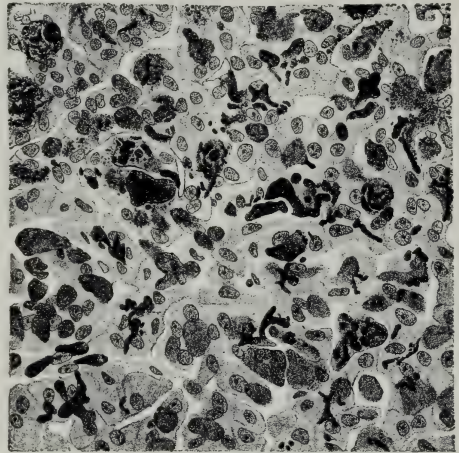


FIG. 13—Bile pigmentation of liver.

The secondary effects of bile pigmentation may be local or general. The local effects are seen more particularly in those cases due to obstruction of the outlet. Under these circumstances, if the obstruction be sufficiently prolonged, fibrosis, as a part of the chronic inflammation of the bile ducts, appears and subsequent to this the fibrosis extends and involves the capsule of Glisson so as to produce fibrosis of the liver itself. This may then go on to actual atrophic cirrhosis. The general secondary effects of jaundice are due to the toxicity of bile itself. Of the important constituents of bile the toxic factors are contained in the bile pigment and in the bile salts. Of these two the pigment is apparently the more toxic and appears to be increased in its toxicity by its combination with calcium or magnesium salts. The important influence of bile is seen in its destructive action upon cells. Toxic doses may produce necrosis of the epithelium of liver and kidney as well as of the muscle of the myocardium. The same action upon the blood may lead therefore to anemia. As was pointed out by Opie and others the injection of bile into the pancreas produces extensive necrosis, and this constitutes the favorite experimental method

of producing acute hemorrhagic pancreatitis. Furthermore, in jaundice there is likely to appear a delayed and imperfect coagulation of the blood. The heart rate is often slowed, blood pressure decreased and sometimes cardiac arrhythmia is observed. The destructive action of bile upon red blood corpuscles is probably contributed to in part by the effect of bile salts in dissolving the lipoids of the erythrocytes; this may also be of importance in the destruction of other cells. The disposition to hemorrhage probably is due to some cytolytic effect upon the blood capillaries as well as to a delay of coagulation. The latter is due to inhibitory action of bile salts upon the conversion of fibrinogen into fibrin, as well as to the utilization of calcium to combine with bile pigment, presumably as an attempt on the part of the body to protect itself against the toxic effect of the bile pigments, which are less toxic in combination than when free. The cytotoxic action of the bile upon the kidney expresses itself in the appearance of albumin in the urine and sometimes in the development of a definite acute nephritis. The slowing of the pulse probably is due to a stimulating action of bile salts upon the vagus nerve. The low blood pressure and cardiac arrhythmia may very probably be due to the direct action of the bile upon cardiac muscle so as to inhibit its full functional activity. Contributing to the depressing effects of jaundice upon the heart is the withdrawal of calcium from the plasma by virtue of its combination with bile pigment. Bile salts also exercise a depressing effect upon the central nervous system and in some cases coma and even paralysis may result. Cases of jaundice also show in many instances a diminished resistance to infection. This does not depend upon the bile itself, for although bile may inhibit the growth of certain bacteria such as pneumococcus, it may favor the growth of other organisms. The diminished resistance to certain types of infection is due probably to the influence of the bile upon the bactericidal activity of the blood.

Although experimental evidence shows that bile in itself is toxic, yet the disturbance of liver function by the obstruction of bile outflow, as well as by the direct toxic action of the bile upon the liver cells must be considered. The liver is an important organ in removing from the blood toxic substances such as ammonia. If such an influence be removed from the general bodily metabolism, there is bound to be an accumulation of toxic bodies which add further to the disturbance produced by the jaundice.

Hemolytic Jaundice.—In the course of many infectious diseases slight jaundice may appear, probably due to the destructive action of bacterial or other microörganismal causes of the disease upon red blood cells. Certainly many such organisms can and do produce hemotoxins. Certain forms of epidemic infectious jaundice are due to the spirocheta *icterohemorrhagica*. In infancy, infection of the umbilical cord or its stump may lead to infective hemolytic jaundice. There is also another form of non-infective jaundice which appears in infancy called *icterus neonatorum*. The cause of this condition is not clearly understood but it is known that the blood plasma in infancy contains a somewhat larger amount of bile than the blood plasma of the adult, and it is presumed that the activity of hematopoiesis incident to extra-uterine

life may play a part in the increase of this bile pigment in the blood plasma sufficient to lead to pigmentation of the skin and other tissues. Another condition of importance possibly depending upon blood destruction, is the disease known as congenital hemolytic icterus. Although sporadic cases occur, this condition usually occurs in families. It does not necessarily affect the patient in early life and may appear as adult years are approached. This condition has been extensively studied by Pearce and his collaborators. There is no obvious intoxication, the patient suffers very little from malnutrition, shows moderate jaundice and an enlarged spleen. Examination of the blood shows moderate anemia and a marked increase in the fragility of the blood corpuscles. In other words, these cells appear to be more susceptible to blood destruction than normal. Although bile appears in the plasma and in the tissues it is not usually found in the urine; nevertheless, the urine and stools show an increased output of urobilin indicating the marked disturbance of bile pigment metabolism. The influence of the spleen is not clearly understood and its enlargement appears to be due principally to the destruction of blood corpuscles; nevertheless, the removal of this organ often is followed by considerable improvement in the patient. This improvement is exhibited not only in the general clinical manifestations but also in the metabolism. The loss of nitrogen, calcium, magnesium, and iron as well as the increased excretion of uric acid, returns almost to normal level following operation. The studies of Hoover and Blankenhorn have served to emphasize the importance of a condition known as *dissociated jaundice*. This is particularly well exemplified in the hemolytic form of jaundice wherein the blood contains bile pigment but not bile salts. The term, however, applies to the presence of either bile salts, or bile pigment, without the other constituent. In cases of obstructive jaundice where both constituents would be present, the excretion by the kidney of bile salts may lead to a dissociated jaundice in which pigment only is present in the plasma. In case of hemolytic jaundice it seems likely that the dissociation is due to the fact that only bile pigment is formed in excess and gains access to the blood. This is advanced as an argument in favor of the idea that in such forms of jaundice the pigmentation may occur quite independently of any participation on the part of the liver. In any case the bile salts are more readily diffusible than are the pigments and are more easily secreted by the kidney.

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CHAPTER III.

DEGENERATIONS AND INFILTRATIONS

INTRODUCTION.

CLOUDY SWELLING.

HYDROPIC DEGENERATION.

FATTY METAMORPHOSIS.

FAT INFILTRATION.

FATTY DEGENERATION.

FATTY ACIDS AND LIPOIDS.

DISTRIBUTION OF FATTY SUBSTANCES IN THE BLOOD.

ADIPOCERE.

THE HYALINS.

HYALINE DEGENERATION.

ZENKER'S HYALIN.

MUCINOUS DEGENERATION.

PSEUDOMUCIN.

COLLOID DEGENERATION.

GLYCOGEN INFILTRATION.

AMYLOID.

NATURE OF AMYLOID.

MODE OF DEPOSIT.

LOCAL AMYLOID DEPOSITS.

Introduction.—Prominent among the retrogressive pathological processes are the degenerations and infiltrations. They are usually discussed together because they overlap in their nature and manifestations. The degenerations are characterized by essential changes in the protoplasm and a coincident interference with function. The infiltrations are changes of the cell in which either waste or other materials are brought to and deposited in the cell; cellular function is sometimes but not necessarily altered. The use of the terms is partly a matter of convenience because most of the degenerations are to some measure also infiltrations. Normal cell form and function, admirably presented in the book edited by Cowdry, are complex and in some respects far from clear. Consequently the discussion of pathological alterations is somewhat involved. It is probable, as will be pointed out, that certain changes, such as cloudy swelling fatty degeneration and certain infiltrations are manifestations of inherent irritability of cells carried on in abnormal degree.

Cloudy Swelling (Albuminous or Parenchymatous Degeneration).—Most conditions which lead to death in man, other than accidental or traumatic causes, result in degenerative changes in various organs or tissues throughout the body. These changes are found in the so-called parenchymatous cells which include the essential cells of glandular and muscular organs, also endothelial cells and leucocytes. The earliest and least severe is called cloudy swelling. Following the appearance of this condition numerous other changes may occur, which finally lead to the death of the cell provided the causative condition is progressive and severe. Virchow first described cloudy swelling and gave it its name. Organs the seat of this condition are somewhat swollen; their tissues have lost the normal lustre and appear more opaque than normal. In well marked cases the organ resembles parboiled animal organs. The swell-

ing leads to tension of the capsule so that when the organ is cut the somewhat swollen substance bulges above the cut edge. The cut surface is pale, soft and friable. If individual cells be teased out and examined fresh under the microscope, the cell is larger than normal, its outline not altogether distinct and the cytoplasm so granular that the nucleus is considerably obscured. If, however, a stained section be examined, the most important changes are increase in size of the cell and increase in granulation of the cytoplasm. In those organs limited by a capsule, the swelling of the cells may, by compression of their margins, make the outline somewhat more distinct than normal. In other instances, even in the stained preparation the lack of definition of outline is apparent. Inasmuch as the sectioning with the knife cuts through the cells, the obscura-

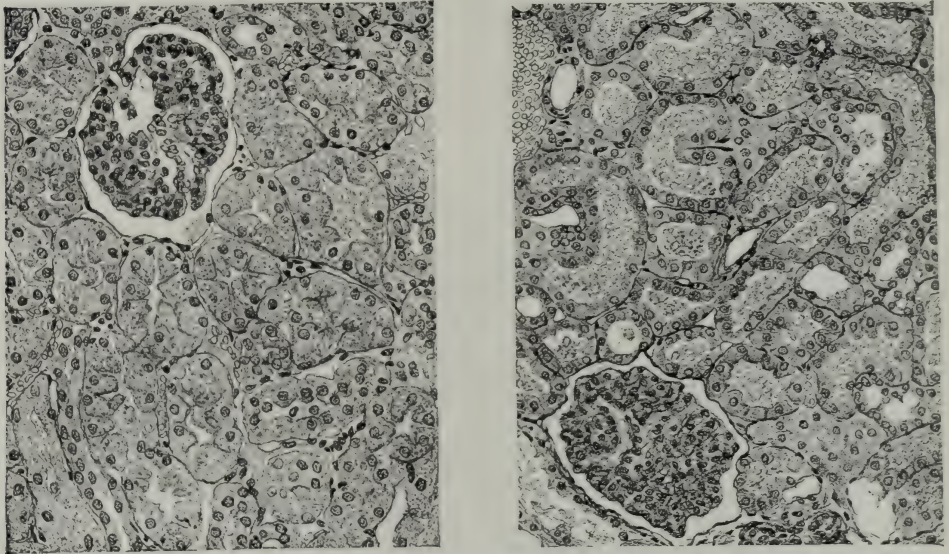


FIG. 14—Cloudy swelling of kidney. The illustration shows the earlier stage in which the cells are swollen, granular and in places occlude the lumen of the tubule. The illustration to the right shows a later stage in which part of the cytoplasm has disappeared, leaving a narrow rim of cells and albuminous granular precipitate in the lumina, representing precipitated protein of the urine.

tion of the nucleus is not likely to be apparent in such material, especially when the nucleus is well stained. The granules, however, are coarser than the normal Altmann granules. In the later stages of cloudy swelling of the renal epithelium it is not unusual to find that the part of the cells nearest the lumen of the tubule has disappeared, and instead of finding the tubule almost completely blocked by the swollen cells, the lumen may be somewhat larger than normal and is outlined by a narrow rim of granular cells. As a rule, in cloudy swelling the nuclei show no definite change but in some instances a condensation of chromatin near the nuclear membrane is observed. When shrinkage, fragmentation, or solution of the nuclei occurs, the condition is no longer cloudy swelling, for these nuclear changes indicate that cell death has occurred.

The poisonous substances of infectious diseases are the most important causes of cloudy swelling. It is extremely rare that an autopsy on a patient dead of infectious disease fails to show well defined cloudy swelling of heart,

liver, kidneys, and other parenchymatous organs. Poisons introduced from without also produce cloudy swelling, notably cantharadin, phosphorus and mercury. The use of these agents is an important means of producing experimental cloudy swelling. Since the earliest change demonstrable in parenchymatous cells following occlusion of the artery is cloudy swelling, reduction of nutrition and oxidation may be regarded as important causes. Similarly, general starvation may lead to a moderate degree of the same change. Extensive surface burns are also complicated by cloudy swelling of the viscera, whether the result of a toxic product of the burn (Weiskotten), concentration of body fluids (Underhill, et al.), or both, not yet being established. Exposure to high temperatures also leads to cloudy swelling. Overwork of an organ may possibly lead to cloudy swelling. It was shown early in the study of this condition that if one kidney be thrown out of function by ligating its artery or vein, the opposite organ when examined in the course of twelve or twenty-four hours, shows very definite swelling of its epithelium. If this occur following the surgical removal of a kidney in man, it is evanescent and quickly followed by recovery.

There has been much study and speculation in regard to the nature of the granules in the cytoplasm. These granules respond positively to the xanthoproteic reaction, which indicates that they are of protein nature. That the granules are not thrown down by a process similar to heat coagulation of protein, is shown by the fact that addition of dilute acetic acid or dilute potassium hydrate to a fresh cell suspension is followed by disappearance of many of the granules. It is true that fever may be accompanied by body temperatures sufficiently high to produce turbidity of protein solutions, yet many afebrile conditions lead to cloudy swelling quite as severe as that observed in fever. Following treatment with dilute acid or alkali, there frequently remains in the cell a number of highly refractile globules which are believed to be of lipid nature and have been called myelin and protagon globules. If the condition be severe, it is also possible to demonstrate small fat globules within the cytoplasm. The lipid and fat globules indicate an advancement of the condition beyond the stage of simple cloudy swelling. Organs the seat of cloudy swelling are reduced in specific gravity and increased in weight, which indicates an imbibition of water. This is further supported by the fact that the percentage weight of dry substance is less in cloudy swelling than in the normal state. It is therefore apparent that the increase in size of the cells depends in part at least upon the taking up of water. There is no positive indication that the salt content of the cell increases, but since the condition is degenerative in nature it is possible that there is an alteration of hydrogen ion concentration toward the acid side. Thus, the cell protein becomes a hydrophilic acid-protein which favors imbibition of water. To explain the formation of granules following the taking up of water, it seems necessary to assume that in the normal condition the cytoplasmic protein is in a state of colloidal solution and that the excess of water alters this sol state to a suspensoid state in which the finer particles of protein agglomerate to produce coarser granules. Davidman and Dolley

have studied the matter most carefully, and conclude that all the phenomena can be regarded as the result of states of cellular excitation and depression incident to a stimulation expressed in any of the causes given above. On this basis the state of depression consequent upon a deficient oxidation leads to progressive failure of cytoplasmic synthesis and the accumulation of unutilized food, as supposed by Virchow. The same lack of oxidation results in products which are difficult to eliminate. It is also possible that nucleolar substance may be discharged into the cytoplasm during a period of excitation. The imbibition of water and these other changes are thus clearly correlated with states of excitation and depression, and the phenomenon of cloudy swelling can be regarded as a physiological process, which on the one hand is easily recovered from, or on the other hand may lead to death of the cell. There is no good ground for assuming that the granules are specifically either altered Altmann granules or mitochondria. Indeed Smith and Rettie find that mitochondria undergo early destruction.

Bell points out that it is impossible from the gross examination of an organ, apparently the seat of cloudy swelling, to state what the microscopical change will be. The microscopic examination of such an organ may show a variety of changes. Sometimes a severe cloudy swelling diagnosed grossly may show relatively little change in the cells microscopically. On the other hand a mild degree of cloudy swelling grossly, may show on microscopic examination severe cloudy swelling, sometimes associated with marked lipoid deposits and even with advanced fatty degeneration. Thus, a gross diagnosis of cloudy swelling is often altered upon subsequent microscopic study. Postmortem degeneration of tissues resembles very closely the changes seen in cloudy swelling and this diagnosis is practically impossible if the body has been dead for any length of time. Nevertheless, postmortem degeneration is likely to show more marked cytoplasmic change and early involves the nucleus.

The functional changes accompanying cloudy swelling may be evident upon clinical examination. It is probable that the low blood pressure in the later stages of infectious disease, depends in part upon cloudy swelling of the myocardium and arterial musculature. It is not uncommon in infectious diseases to find albumin in the urine, sometimes accompanied by a moderate number of casts. As the infection subsides this condition usually clears up readily, and by comparison with experimentally produced cloudy swelling of the kidney, it is safe to assume that many of these cases represent merely cloudy swelling of the renal epithelium. It is also probable that some of the digestive disturbances in acute infectious disease depend upon cloudy swelling of the digestive glandular epithelium. With considerable severity and long duration of the infection, these minor changes in the parenchymatous cells may become more severe, but if cloudy swelling be uncomplicated the outlook is extremely good, provided the cause be removed.

Hydropic Degeneration.—Cloudy swelling as has been stated, exhibits imbibition of water, and hydropic degeneration differs only in degree. It is a term used conveniently to designate a condition in which the water is present

in numerous droplets so as to dominate the picture of the cellular change. The same general causes operate to produce hydropic degeneration as noted in connection with cloudy swelling. Grossly, the organs have the same general appearance as is seen in cloudy swelling except that they may be softer and more friable. Microscopically small or large globules appear within the cytoplasm, rarely within the nucleus. In certain instances, particularly where the hydropic degeneration occurs in the neighborhood of inflammation, and in the earlier stages of central necrosis of the liver, it is possible, as Mallory has pointed out, to demonstrate small accumulations of fibrin within the globules. This deposition probably results from the elaboration in the cells themselves of a fluid characteristic of inflammation. Fibrin separates out and the fluid which remains is serum. This type of lesion is the result of excitation with greater dynamic response than occurs in simple cloudy swelling. It is unlikely that the simpler changes do any permanent damage to the cell, but in the case of inflammatory involvement the injury may more readily lead to death of the cell.

Fatty Metamorphosis.—Human fat contains the unsaturated oleic acid and the saturated palmitic and stearic acids. The combination of these to form the body fat differs in different parts of the body but in a general way is fairly constant. As age advances the oleic fat increases relatively in amount. The constitution of fat is also influenced by the diet. Under normal conditions much of the fat of the body is derived from that in the food, and if conditions be distinctly abnormal, the food fat may be in part reproduced in the fat storehouses of the body. For example, if a dog be starved and then fed with fat different from that of his own body, the subsequent accumulation of fat is similar to that in the food. Although normally the carbohydrates are oxidized by the body more readily than the fats and therefore serve to protect fat accumulations, nevertheless, it is known that fat can be formed from carbohydrates. Inasmuch as the fat molecule is considerably larger than the carbohydrate molecule, it is assumed that the synthesis takes place through the medium of lactic acid formation. The body protein is protected primarily by consumption of carbohydrate and secondarily of fat. Protein may be utilized in normal body metabolism but to only a small degree. Much of the earlier conception in regard to pathological fat changes rested on the belief that fat can be formed from protein. This assumption was made by Virchow. The prevailing view at the present time is that protein may be regarded as a possible source of fat, but there is little reason for believing that it generally serves this purpose under normal or even pathological conditions.

Fat accumulates in the body and is stored in certain depots. These include the subcutaneous tissue, the omentum, the liver, the retroperitoneal structures, the grooves of the heart and certain other situations. With the exception of that deposited in the liver the fat is found only in connective tissues. The embryonic fat cell shows the fat in the form of small globules in the cytoplasm, but in the adult type it is present in the form of large globules which may constitute the major portion of the cell. When fat is absorbed from the intestinal

tract it is broken down into fatty acids and glycerol, both of which are diffusible substances, but the action of lipase soon reconstructs the fat molecule. Finally, the fat may be broken down by oxydase, with the liberation of energy, or it may be stored. If stored, it is subsequently broken down by lipase into fatty acid and glycerol for transport, and when it reaches the points at which it is to be utilized it is again synthesized into fat by the action of lipase. It must be clearly understood, however, that in the final utilization of fat in metabolism, the influence of oxygen is essential. If the oxidizing capacity of the body be good, it may reasonably be expected that fat catabolism can be readily accomplished, but if oxidation be inadequate the breaking down of fat may be interfered with and it accumulates in the depots.

It is customary in studies of pathology to distinguish between fat infiltration and fatty degeneration. This differentiation is usually readily made except in certain border line cases. There are confusing elements which will be referred to later, but for the sake of simplicity it is desirable to recognize these terms. Fat infiltration signifies either an increase in the amount of fat normally present, the presence of fat in organs between the parenchymatous cells, or, as in the case of the liver, the presence of abnormal amounts of fat within the liver cells. The use of the term fat infiltration signifies that little damage has been done to the cells and that little functional disturbance may be expected. Fatty degeneration on the other hand, is a condition in which fat is deposited within parenchymatous cells, accompanied by other degenerative changes within the cells. In this condition functional disturbance is usually severe.

Fat Infiltration.—This condition can best be discussed by describing its appearance in several organs. In the heart, for example, there is normally a certain amount of fat in the subepicardial connective tissue, particularly in the grooves of the heart and along the right border of the right ventricle. Normally this fat is confined to the subepicardial connective tissue and it is easily possible in cross section to distinguish a sharp line of differentiation between the fat and the myocardium. Under certain conditions, however, the fat may appear between the muscle fibers of the myocardium and ordinarily this is found to be an extension downward into the myocardium from the fat of the epicardium. This process is confined to the connective tissue elements between the muscle fibers; it does not involve the heart muscle itself and is therefore regarded as an infiltration. Similarly in the pancreas, the fat is normally present only beneath the peritoneum and around the borders of the organ. In fat infiltration the fat is found in the connective tissues between the lobules of the pancreas, separating them and producing an enlarged, fat, greasy organ. The liver is the one human organ in which fat infiltration occurs in the parenchymatous cells. The liver of fat infiltration is a large, pale yellow liver with rounded edges and a tense capsule. It cuts with normal resistance and greases the knife. The cut surface is greasy and yellow with little gross differentiation of lobules. Microscopically, the liver shows the fat in the form of large globules. Fat accumulation is so great that the cytoplasm of the cells is pushed aside to form a thin rim about the fat globules and the nucleus is pushed off to one side, thus

producing the "signet ring" cell. In the earlier stages the fat is found in the peripheral cells of the lobules, but as the process advances all the cells in the lobules may be involved. In those organs where fat infiltration appears in the connective tissue, the parenchymatous cells may be unaltered or the seat of moderate atrophy and the connective tissue cells between these parenchymatous elements show fat as it appears in fatty connective tissue. Fat infiltration primarily depends either upon the feeding of fat in excess or reduced oxidation so that normal amounts of fat cannot be disposed of in the body. Under certain pathological conditions, however, this general rule may not apply, as, for example, in those cases where the body itself is emaciated but the liver shows a very large amount of fat. A physiological increase of fat is seen in the later months of pregnancy and during lactation. In such people the accumulation of fat is not likely to be excessive. In alcoholism, fat accumulation is of common occurrence. The explanation of this is not absolutely clear but it is important that in the liberation of energy the organism seizes upon the most readily oxidizable substances. Alcohol is oxidized readily and supplies considerable energy; the fats are thus protected and, not being oxidized, accumulate in the body. Another explanation is to the effect that alcohol depresses general oxidation and therefore prevents proper utilization of the fat. Similar substitution of more easily oxidizable substances for fat in the liberation of energy may occur when

the food ratio is so poorly balanced that although it contains a normal amount of fat, it contains also an excess of carbohydrates which may be burned readily and thus protect the fat. Deficient oxidation may depend upon some obscure congenital predisposition or upon alteration of function of some of the ductless glands. The congenital cases appear in those individuals who in spite of reduced diet and increased exercise remain fat. The opposite condition is seen in those who in spite of extremely rich diet always remain thin or accumulate only small amounts of fat. Waldvogel demonstrated that if B-oxbutyric acid be injected into lean persons there is a slight elevation of temperature and complete combustion of the acid without the appearance of any of its products in the urine. In obese individuals, on the other hand, this relation is altered; they show no rise of temperature, probably because the oxidation of the acid is slower; they show acetone in the urine and its odor may be detected in the breath. This indicates that in the obese individual the

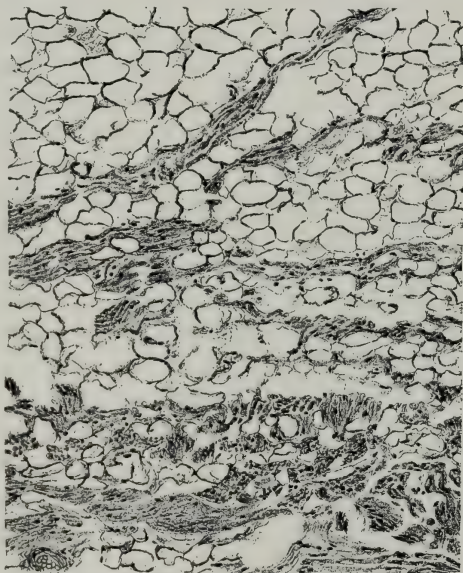


FIG. 15—Fat infiltration of heart. The fat appears between the atrophic muscle fiber cells.

reduced and slow oxidation is insufficient to metabolize the fatty acids and as a result neutral fat accumulates in the tissues. In connection with abnormal transport of fat as a result of disease, it may be mentioned that many tuberculous individuals when they come to autopsy show fat infiltration of the liver, in spite of the fact that they are considerably emaciated. Not infrequently tuberculosis of cattle leads to an increased general deposition of fat and occasionally the same phenomenon may be seen in man. In human cases, however, where only the liver shows the fat accumulation, it is difficult to say whether this represents the transport of fat from other parts of the body or whether it is due to the large amount of fat in the diet of tuberculous patients.

The functional disturbance due to fat infiltration depends largely upon the degree of infiltration. It is possible that in excessive fat infiltration of the heart, its function may be disturbed. The same may be true of pancreas and of liver. Nevertheless, in these cases other changes are present, such as atrophy of parenchymatous cells, and it is possible that whatever functional disturbances are demonstrated, are due rather to the atrophy than to the fat accumulation.

There are several forms of obesity that deserve mention at this time. In the preceding paragraph it was noted that there are certain individuals who congenitally are unable to utilize their fat. The obesity of these individuals is usually moderate but in exceptional cases may be severe. This condition is often referred to as *adiposis simplex*. *Adiposis dolorosa* was described by Dercum and is often called Dercum's disease. Patients with this affection show a large accumulation of fat, particularly about the upper part of the trunk, the shoulders and the axillæ, which is usually tender to pressure and occasionally spontaneously painful. *Adiposis cerebialis*, *adiposis genitalis*, or Fröhlich's syndrome is likely to show only moderate deposition of fat. Although the patient may attain good stature and be highly intelligent, the conformation of the body is likely to be of the feminine type in males as well as in females. The genital organs are ill-developed, and in the males the sex characters are altered more particularly in the scanty growth of hair in the axilla, on the pubis and on the face. In females the alteration of sex characters is seen especially in small size of the breasts and genitalia. *Adenolipomatosis* is a much more unusual condition in which the fat deposits may be either general or in the form of large tumor-like accumulations rather widespread over the body. This condition is characterized histologically by the appearance of many lymphocytes in fat tissue, which may accumulate and form masses resembling small lymph nodes. These types of obesity by no means include all its forms, for from time to time cases are reported which cannot be classified in any of these groups. Obesity often appears to depend upon disturbances of the ductless glands. Of these glands the pituitary is involved in a certain number of the cases while in others the thyroid appears to be the disturbing factor. Recent studies would indicate that in many cases of obesity, there is a considerable alteration in water metabolism. Certainly in some of the thyroid cases there is extensive edema of the tissues in addition to the fat deposits, and it seems likely that in other cases the same condition in a less notable degree may be present. In obese individuals

consumption of large quantities of water may result in an increase of weight which does not disappear for several weeks after the period of excessive consumption. This problem has not as yet been thoroughly investigated but it is important to bear in mind that at least in part the weight of these persons depends upon water retention (excellent discussion by Lyon).

Fatty Degeneration.—As can be understood from the above paragraph, fat infiltration affects cells which normally contain fat and represents an alteration simply of the normal fat depots and fat transport. Fatty degeneration on the other hand is a deteriorative process in the course of which fat becomes apparent in the cells. This change affects not only these cells which are concerned with the normal metabolism of fat but may attack any of the cells of the body. Both from the viewpoint of function and that of prognosis fatty degeneration is far more serious than is fat infiltration. The causes of fatty degeneration are very much the same as those which produce cloudy swelling, except that they operate either over a longer period of time or with greater intensity. The more severe or the more prolonged infectious diseases are likely to produce not only cloudy swelling of the parenchymatous organs but fatty degeneration as well. Prolonged or severe general anemias such as pernicious anemia are likely to show fatty degeneration of heart, liver, kidney, and other organs. The same may be true of more marked degrees of secondary anemia. Similarly, local anemias may lead to fatty degeneration. In the case of infarction, the area directly involved is the seat of death of the tissue, but the margins of the infarct may show fatty degeneration, probably because these marginal cells synthesize fatty acids and glycerol which have diffused out of the dead area. The introduction of a variety of poisons including phosphorus and hydrazin, as well as mercury and several other metallic poisons may also lead to fatty degeneration. Severe diabetes which shows not only alteration of carbohydrate metabolism, but also that of fats, may show fatty degeneration of organs, particularly the kidney.

The gross appearance of an organ, the seat of fatty degeneration, is somewhat variable dependent upon other associated conditions which may be present. In a fairly typical case the organ is soft, flabby, may be considerably reduced in size and in the case of an encapsulated organ shows a flaccid capsule. It cuts with normal or reduced resistance and the cut surface is soft, bulging, moist and distinctly friable. The color of both the outer and the cut surfaces is yellow. In the heart, the yellow may be distributed irregularly and when viewed through the endocardium, the patches of yellow may form small lines separated from each other so as to produce a "tabby cat" or "tigroid" appearance. In the liver the central zones of the lobules are particularly the seat of this change. In the kidney, fatty degeneration appears rather in the cortex than in the pyramids. Microscopically, the cell the seat of fatty degen-

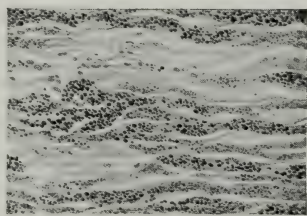


FIG. 16—Fatty degeneration of heart muscle. Stained with osmic acid the blackened globules of fat appear within the muscle fiber cells.

eration is variable in size, sometimes slightly increased because of the accompanying cloudy swelling and sometimes reduced. There is always present some form of degeneration other than the fatty change and this is most commonly cloudy swelling. Therefore, the cytoplasm is usually granular. The fat is present usually in the form of small globules. The nucleus may exhibit no change whatever or may show a peripheral disposition of the chromatin similar to that seen in some cases of cloudy swelling. Occasionally the chromatin shows a failure to take the basic stain and therefore may be regarded as being in an early stage of solution. In contrast to fat infiltration, fatty degeneration affects particularly the parenchymatous cells. It therefore is likely to be confused with fat infiltration only in the liver. In this organ, in addition to showing small globules, fatty degeneration usually affects the cells of the central zone more markedly than those of the peripheral zone, and the associated degenerative changes are of great importance in making the diagnosis. It is quite true that fat infiltration may also appear in the form of small globules, but this change is more marked in the peripheral zone, and unless complicated in some way is not associated with degenerative changes. It is extremely rare that fatty degeneration shows such a great accumulation of fat in the cells as to push the nucleus to one side, as is the case in fat infiltration. It is probable, according to Wells, that the fat globules accumulating in a normal cell, agglomerate by the pressure of the relatively firm cytoplasm to form a single large droplet, but in the degenerate cell the consistence of cytoplasm is reduced and the small droplets of fat remain discrete. However, the old idea, namely that when the globules are smaller than the nucleus, fatty degeneration is present, does not meet acceptance in view of more modern studies. Fatty degeneration affects not only the heart, liver and kidney, but practically all the glandular organs of the body, the blood vessels, voluntary and involuntary muscles and nerve tissues.

The nature of fatty degeneration has been under discussion for many years. At first it was assumed that the fat appearing in these cells was the result of decomposition of the cellular proteins. As studies of metabolism were pursued, it became apparent that protein produces fat under only the most unusual circumstances, and many consider that fat in the animal economy cannot be derived from protein. Experiments were conducted by Rosenfeld to determine whether or not the fat in fatty degeneration may be the product of intracellular activity or the result of fat transport. He poisoned a starved dog with phosphorous and fed the animal with a fat which subsequently could be identified by its melting point and other special characters. Under these conditions it was found that the fat in the liver of phosphorous poisoning was for the most part the ingested fat. This experimental demonstration has often been construed to indicate that the fat in fatty degeneration is accumulated solely as the result of transport. The condition was further studied by the examination of organs chemically, and in the case of the kidney it was found that this organ can exhibit fatty degeneration without a quantitative increase in the amount of fat present by chemical examination. This signifies that fat may be present

in tissues without being demonstrable by microscopic methods and that it may become so altered under the conditions that lead to fatty degeneration that it becomes visible. It was then noticed that the digestion of tissues with pepsin results in the alteration of the fat so as to render it visible. This phenomenon is spoken of as fat phanerosis. It is not to be assumed, however, that digestion is the change by which fat becomes visible in fatty degeneration. It is due rather to some other degenerative change in the cell. Cruickshank points out that autolysis does not lead to the formation of fat. Fischer offers the hypothesis that the normal fat of a cell is present in extremely fine emulsion protected by the protein and salts of the cells. As the cytoplasm undergoes degeneration the condition of the protein may be altered by the presence of acid. The subsequent change which renders some of the protein hydrophilic leads, as has been said before, to cloudy swelling, but as this change becomes more prominent the protective action of the protein which maintains the emulsion is removed, so that the fat may collect into globules which are visible microscopically. Although, in the case of the kidney, fatty degeneration may occur without any increase in the fat content of the organ, yet in the case of heart, pancreas and liver this is frequently not true, and in these organs the degeneration is likely to be accompanied by a distinct increase in fat content which, in the case of the liver, may be extreme. In fact, in experimental phosphorus poisoning, fat may amount to seventy-five per cent. of the dry weight of the organ.

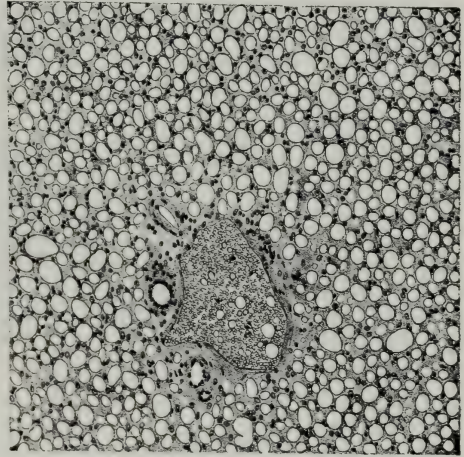


FIG. 17—Fat infiltration of liver. The large vacuoles which appear in the cells lying near the portal space represent fat which has been dissolved in preparation of the tissue.

If, then, it is known that cells may show fatty degeneration because of cytoplasmic changes and further, that cells may exhibit in fatty degeneration the presence of fat brought there by transport, it is reasonable to suppose that in the case of those organs where the fat content in fatty degeneration is markedly increased over the normal, there must be considerable transport of fat to the tissue. Tissue cultures have been studied in reference to fat changes in cells. Lambert found that the amount of fat in the cells is roughly proportional to that in the medium. Foot, however, thought he could see direct transformation of cell granules into fat, and Lewis maintained that fat is formed in cells growing in fat-free media. Nasu is doubtful that the material in the cells is fat and found that cells living, or perhaps vegetating, in salt solution show no such globules. Nevertheless, the work in general indicates that some cellular endogenous mechanism can elaborate fat. In general then, it may be stated that the fat of fatty degeneration is in part fat rendered visible by some sort of phanerosis

and in part fat transported from other situations. In fatty degeneration there is an increase in water content of the part, distinctly more marked than in the case of fat infiltration. Furthermore, in fatty degeneration there is likely to be a decrease in the amount of protein present in the organ. Both these changes are in keeping with the hypothesis offered by Fischer.

The work of Oppel and others, quoted by Dietrich and Kleeberg, would indicate that fatty changes in cells are fundamentally the result of response to various stimuli. Thus, as in cloudy swelling, fatty changes probably represent phases of excitation and depression, exhibited by an endogenous formation of fat within the cell, in part from material brought to it.

It was pointed out in the section on cloudy swelling that there are sometimes present in this condition doubly refractile globules in the cells. This material is likely to be present in greater amounts in fatty degeneration than in cloudy swelling. Neutral fat is singly refractile and is spoken of as isotropic in contrast to these anisotropic droplets. This anisotropic substance is called myelin



FIG. 18—Gross appearance of fatty degeneration in papillary muscles of heart.

and is probably identical with protagon. The chemical analysis shows that it consists chiefly of cholesterol esters combined with variable amounts of phosphatids, fatty acids, soaps, and neutral fats. The constitution varies under different circumstances and the change is to be regarded as a degenerative process affecting the fat and lipoids of the cells. It is possible that the physical changes leading to liberation of fat also disturb the balance of fat, protein and lipoids so that the lipoid material accumulates in the form of microscopically visible droplets. Quantitative studies of the lipoid content of organs, the seat of cloudy swelling and of fatty degeneration, have not yet been made in sufficient number to determine positively whether the lipoids are actually increased in amount or not. Determinations on the basis of histological studies are not accurate in regard to either fats or lipoids. Particularly is this true of lipoids, since the differential staining of these substances is subject to greater errors than is true of the fat stains.

The disturbances of function connected with fatty degeneration are in part dependent upon the causative agents operating in various other ways. There is no doubt, however, that fatty degeneration may result in serious

reduction of functional activity. This can be seen particularly well in the case of fatty degeneration of the heart, which is often associated not only with low blood pressure and pulse pressure but also with cardiac arrhythmia. Similarly fatty degeneration causes disturbance of renal function. In the more moderate cases of chronic glomerulonephritis, the changes in the interstitial substance and in the glomeruli may be relatively slight, and cloudy swelling and fatty degeneration of the epithelium are the most striking changes seen. Deficiencies of elimination are likely to be severe in this disease. In fatty degeneration of the liver there may be marked changes in protein metabolism, particularly in those cases where the lesion is severe. The disturbance of metabolism is seen particularly well in cases of accidental phosphorus poisoning and in acute yellow atrophy of the liver.

Recovery from fatty degeneration of an organ depends in large part upon the possibility of removing the cause. In young individuals where fatty degeneration is the result of infectious disease, recovery commonly occurs, but it may take months and years before all the functional defects are removed. As age advances, the possibility of recovery is decreased. With continued activity of the cause, fatty degeneration not infrequently is followed by death of the cell.

Fatty Acids and Lipoids.—The first products of decomposition of fat are glycerol and fatty acids. This alteration occurs both normally and pathologically. Under the latter condition the fatty acid may be deposited in crystalline form or it may be combined with alkali to form soaps. Both these changes are seen in necrosis of abdominal fat, due to ferments liberated by necrosis of the pancreas. Fatty acids are also demonstrable in decomposed pus of old abscesses, sometimes in gangrene and in the material from bronchiectatic cavities. They have been reported in certain degenerations of the central nervous system and in cases of chronic appendicitis. Fatty acids are of common occurrence in atheroma of blood vessels. It is maintained by Klotz that the fatty acids combine with alkali to form soaps in this condition and that calcium deposit leads to subsequent calcification in these areas. Chemical examination by Wells fails to confirm this series of events. Fatty acid crystals are demonstrable microscopically in tissues which have not been subjected to the action of fat solvents; hence frozen sections are best adapted for this purpose. Copper acetate produces a green color in the fatty acids which is turned black by the addition of hematoxylin. In tissues which have been embedded in paraffin or



FIG. 19—Fatty degeneration of kidney, showing the osmicated fat globules lying near the basement margins of the cells.

celloidin the crystals are dissolved out, leaving acicular spaces in the tissues. Sometimes these crystals or spaces are partly or completely surrounded by multinuclear giant cells, which form as a response to the irritation of the substance and apparently attempt to remove or encapsulate the crystals.

Cholesterol occurs normally in bile, nerve tissue, blood, and in smaller amounts in all the tissues of the body, either free or in combination with fatty acids. Under pathological circumstances the amount of cholesterol may be increased or decreased and certain conditions lead to crystallization of this substance. The crystals are large, flat, rhomboid plates, with fractured re-entrant corners. These are dissolved by embedding in paraffin or celloidin but can be seen in fresh tissues. Treatment of the tissues with four parts concentrated, H_2SO_4 , and one part water produces color in the margin of the crystals, at first red and then violet. Treatment with concentrated H_2SO_4 with a trace of iodine gives rise to a sequence of colors, first violet, then blue, green and red.

Distribution of Fatty Substances in the Blood.—Whilst extensive discussion of these materials in the blood belongs properly to texts on biochemistry, it may not be amiss to indicate some of the essentials here. The subject has been studied since the time when fat was observed grossly in the blood of diabetics and, as chemical methods of study have improved, a great mass of literature has accumulated. In 100 cc. blood, Bloor finds in normal men and women about 0.10 to 0.15 gram of fat in the plasma and from none to 0.15 gram in the corpuscles, usually distinctly less in corpuscles than plasma; of total fatty acids about 0.30 to 0.40 gram, somewhat less in the corpuscles than in the plasma; of the lecithin group about 0.30 gram, that of the corpuscles being approximately double that of the plasma; of cholesterol 0.19 to 0.25 gram, about equally distributed between plasma and corpuscles. Somewhat different figures are given by Oser and Karr. Feeding fat not only increases the fat of the blood but also the lecithin group. Bloor's investigations "have shown that lecithin probably takes an active part in fat metabolism as the first stage through which fats pass in their utilization by the organism." The ratio between total fatty acid and lecithin is fairly constant as is also that between lecithin and cholesterol. The latter consideration makes it probable that cholesterol or its esters also play a part in fat metabolism.

The determination of fats, including the glycerides of fatty acids and the neutral fats, is difficult, but increases are noted during fat absorption from the intestine and have been reported in nephritis and in the lipemia of diabetes. The total fatty acids increase during fat absorption and are said to increase in fasting and during anesthesia; the increases in the last two conditions are not constant and probably depend upon the nutritional condition of the animal. Exercise, nephritis, pneumonia, pregnancy, and in animals, experimental anemia, are accompanied by increases of the total fatty acids. In diabetes mellitus the total fatty acids are usually but not invariably increased during a period of acid intoxication. The same is true of diabetic coma. Although it has been suggested that the increase is due to cell disintegration,

it seems more reasonable to suppose that it is due to inability of the organism to utilize the accumulated or ingested fatty substances. The phosphatids, including lecithin, cephalin, etc., are increased during absorption of lecithin and of fat. Diabetes usually shows increases during the periods of acid intoxication, but this is not constant even when coma appears. In nephritis both high and low values have been reported; in leucemia high values are reported, confined, however, to the corpuscles; syphilis shows high values in the serum; and in cachexia from carcinoma low values are reported. Experimental anemias in animals, the result of repeated bleeding and also excision of the pancreas, as well as the severe human anemias (Oser and Karr), show increases of this group of lipoids.

Cholesterol exists in the blood, free and in the form of esters. Although it is an alcohol, cholesterol may combine with fatty acids to form fats and is increased by feeding animal foods, particularly eggs, butter and meat. Bloor, however, finds that fat alone does not increase the cholesterol in the blood. Pathologically the cholesterol follows closely the levels of other fatty substances. Myers summarizes the alterations as follows: The cholesterol content of the blood is lowered by a diet poor in lipoids and by high body temperature. It is increased by a diet excessively rich in lipoids, by diseases such as diabetes, arteriosclerosis, nephritis, and during pregnancy, beginning at about the fourth month and lasting for a variable period after delivery. It is also increased in alcoholism, narcosis and syphilis. The increase in diabetes is inconstant as is true of the other fatty substances. Decreases have been noted in various types of cachexia. Jaundice due to complete obstruction of the bile duct leads to an increase of blood cholesterol probably because of failure of elimination in the bile, whereas jaundice due to partial occlusion of the bile duct as well as hemolytic jaundice shows no increase. Claims have been made that gall stone disease in man is fairly regularly associated with an increase in blood cholesterol. Dewey has shown experimentally that hypercholesterolemia in rabbits may lead to gall stone formation, but Denis as well as Reimann and Magoun have shown that the two conditions are not constantly or even frequently associated in man.

Bloor draws attention to the irregularity in behavior of the fatty substances of the blood in pathological conditions. While no set of changes is constant, yet "the most characteristic feature of pathological conditions in human beings is the increase of 'total fatty acids' and 'fat' both in plasma and corpuscles, and the decrease of 'lecithin' in the plasma. Since the 'fat' is probably to be regarded as the inactive form of the body lipoids [including all the fatty substances], the form in which they are stored—the raw material of fat metabolism—and the 'lecithin' as the first step in its utilization, an undue accumulation of 'fat' or a notably decreased value for 'lecithin' probably indicates a diminished activity of the fat metabolism."

Adipocere.—Obese corpses buried in wet ground are sometimes partly converted into a soap-like mass which preserves the general conformation of the body. As a rule the face and the distal parts of the extremities are only

poorly if at all preserved. This material is resistant to bacterial decomposition and the corpse may retain its general form for many years. Early studies of the condition were interpreted to indicate that the muscle and other tissues are converted into fat and then into soap, but more recent studies indicate that the soap is formed entirely from the body fats. The fats are split by bacterial ferments during decomposition and possibly also by the lipases of the body. The glycerol diffuses and the fatty acids combine with the ammonia of decomposition to form the soluble ammonium soaps, which flow into and replace the decomposed muscle. Subsequently, slow reaction with calcium and magnesium salts produces the firmer and less soluble soaps of these metals. The condition is seen in ground not only moist but rich in lime. The calcium may come from both the body and the ground or water.

Fat Stains.—Embedding tissues in paraffin or celloidin involves the use of fat solvents, so that tissues after this treatment no longer contain visible fat. Vacuoles in such tissues can often be inferentially interpreted as indicating the presence of fat, but other substances may also produce vacuoles and the diagnosis is not always secure. Frozen sections of fresh or formalin fixed material are used for the special stains for fat. Bell and also Bullard have pointed out that the use of formalin so alters the fat that some of it stains with basic dyes and some does not stain either with these dyes or the special stains. For accurate work, therefore, only fresh unfixed tissues should be used. Scarlet R and Sudan III stain neutral fats of the olein, palmitin and stearin types. Herxheimer uses Scarlet R in alkaline alcoholic solution and Burgess recommends alkaline alcoholic solution for Sudan III. These solutions stain more rapidly and intensely than the neutral alcoholic solutions. In either case Scarlet R stains the fat red and Sudan III stains it orange. Both operate by virtue of the fact that they are fat soluble and permeate the fat more readily than the tissues. Osmium tetroxide (OsO_4) (osmic acid) is reduced to OsO_2 by unsaturated fats, giving the fat a dark brown or black color; it is therefore of use in human pathology only for demonstrating oleic fats. It is employed in 1 per cent. or 2 per cent. solution in water, preferably not in combination with chrome salts or other oxidizing agents. With Nile blue sulphate, neutral fats are stained red by the oxazone base, whereas fatty acids are colored blue by the formation of blue colored soaps with the oxazine base of the dye. Mixtures of neutral fats and fatty acids stain in various shades of purple. Fatty acids and soaps form a green salt if stained with neutral copper acetate, and hematoxylin turns this deep blue or black. The so-called myelin and other cholesterol-fatty acid compounds are doubly refractile when viewed with Nicoll prisms. Lipoids in the narrower sense may be demonstrated by the Ciaccio and by the Lorrain Smith-Dietrich methods. Both depend on fixation with potassium bichromate. The Ciaccio method employs Sudan III in alcohol-acetone which stains the lipoids orange-red or orange-yellow. The Lorrain Smith-Dietrich method utilizes hematoxylin and a borax-potassium-ferrocyanide solution, by which the lipoids are stained blue-black. The Golodetz reaction for cholesterol depends upon the fact that formol-sulphuric-acid vapor stains fats, fatty acids

and cholesterol brownish-red; further treatment with the vapor of osmic acid makes no change in the cholesterol but deepens the tint of the fats and fatty acids.

In gross preparations the presence of fat may be demonstrated or emphasized by the use of Scarlet R and Sudan III. Immersion of a piece of aorta in solutions of one of these dyes may emphasize the fatty changes in areas of atheroma. Beautiful demonstrations of infiltrating cancers of the breast may be made by staining the fat of this organ.

The Hyalins.—Under pathological conditions there may appear in tissues a clear, homogeneous, structureless material which is described by the term hyalin. Grossly, the material is usually somewhat translucent or glassy and transmits the underlying color of the organ. The term is a broad descriptive term and includes in its scope a considerable number of substances which have these physical characters. By virtue of gross, microscopic and chemical reactions, it has been possible to separate and to differentiate certain particular forms which have a special character. These include mucin, colloid, glycogen, amyloid and several other clear structureless materials. The features which differentiate these special forms of hyalin will be described in connection with the discussion of the particular topics. In order to be specific in the application of terms, it is well to refer to that form of hyalin which is not to be differentiated by special characters as simple hyalin.

Hyaline Degeneration.—The most common and the most widespread of the simple hyalins is that appearing in connective tissue. This may be found in dense tissue in old people, it may be seen in old scars and in situations where connective tissue is laid down as part of chronic inflammation. It is similar in all probability to the hyalin of cartilage and yellow elastic tissue. Grossly, this material is often seen in the thickened pleura of chronic pleurisy, in the thickened capsule of the spleen and in certain stages in the process of arteriosclerosis. To the naked eye it is clear, homogeneous, structureless material and often has a faint blue tint. Histologically the nuclei are seen scattered somewhat sparsely about the tissue and between these is the homogeneous material. This connective tissue hyalin is seen particularly well in chronic inflammation of lymph nodes where it was first described by Von Recklinghausen in connection with chronic tuberculous lymphadenitis.

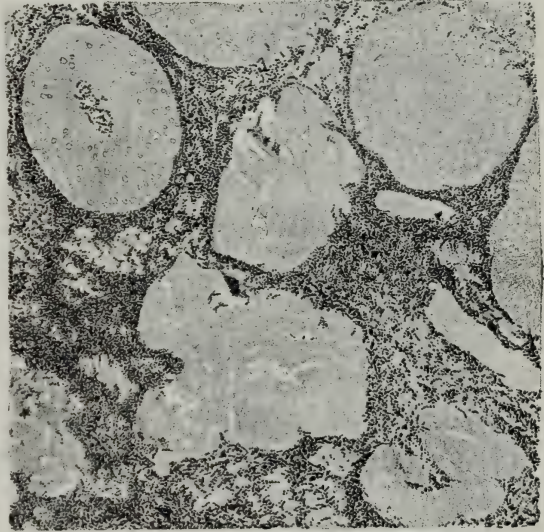


FIG. 20—Hyaline degeneration of lymph node
(Von Recklinghausen).

Epithelial cells are also capable of producing hyalin. This may be seen in the form of droplets within the cytoplasm of the cells and is especially well exemplified by the presence in tumor cells of the so-called Russell fuchsin bodies. At first supposed to be the causative organism of tumor formation, these bodies were subsequently shown to be simple degeneration products of the cells. Similar bodies may be found in plasma cells and in the connective tissue cells of granulation tissue. In these situations Brown, and also Saltikow, believe that the hyalin represents ingestion and transformation of blood cells, but this view is not generally held and is specifically contradicted by McConnell and Lang. In the epithelial cells of the central zone of the liver, particularly in that form of cirrhosis believed by Mallory to be of alcoholic origin, hyaline droplets are frequently found. In the late stages of acute and in the chronic stages of Bright's disease, hyaline droplets are often formed in the cytoplasm of the tubular epithelium, particularly of the convoluted tubules. The urine of cases of Bright's disease shows casts, among which are included the hyaline casts. These are also seen in histologic sections of kidneys of this type. The origin of this hyalin is not exactly known, but it seems probable that it is extruded from the tubular epithelium in the form of droplets and condensed in the tubules to form the casts. A peculiar tumor known as the cylindroma is characterized histologically by the presence of hyaline cylinders. These apparently are produced by the cells which surround the cylinders. It is not definitely known whether these cells are epithelial or endothelial in character but it seems

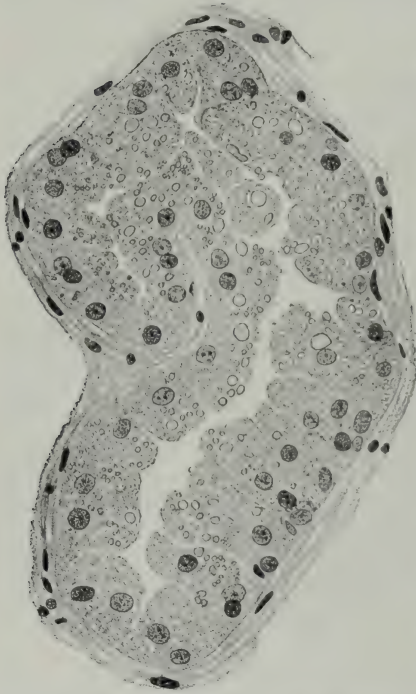


FIG. 21—Hyaline droplets in renal epithelium.

likely that the hyaline substance is produced by the cells. The keratinization of cutaneous epithelium is also a form of hyaline change.

In connective tissue hyalin there is apparently a retrogressive physical change whereby the fibers of the connective tissue fuse to form the hyaline masses. Similarly, red blood corpuscles may conglutinate to form hyaline masses. Fibrin threads may similarly fuse. In certain types of necrosis (local death of tissues) small groups of cells of epithelial or other character may fuse to form hyaline areas. Blood clots may undergo similar change. In all these instances, it appears that the important alteration which occurs is physical rather than chemical, because the hyaline material retains essentially the same chemical constitution as the parent substance.

The important known characters of simple hyalin are physical rather than

chemical. The fact that certain forms have been differentiated by chemical examination leads to the hope that further differentiation will be possible. Goodpasture draws attention to the fact that certain hyalins may be crystallized in the cells. The crystals behave toward solvents and other chemicals in the same way as does the non-crystallized material. This may mean that whereas the simple hyalins show variation of composition, yet probably each form has a fairly definite chemical structure. Unless methods of isolation of these substances in quantity are devised, much of the future investigation depends largely on microchemical technique.

Zenker's Hyalin.—In cases of typhoid fever, influenza and numerous other acute infectious diseases, the voluntary muscles sometimes undergo a change which is known as Zenker's degeneration, waxy degeneration, or Zenker's hyalin or Zenker's hyaline necrosis. This change is particularly likely to affect the rectus abdominis muscle, but may occur in other skeletal and in cardiac muscle. In the well marked cases it is easily visible grossly and the muscle appears pale and translucent; not infrequently it is associated with partial or complete rupture of the muscle. Microscopically, the muscle fibers are found to be swollen, scattered, often fractured, and instead of the usual

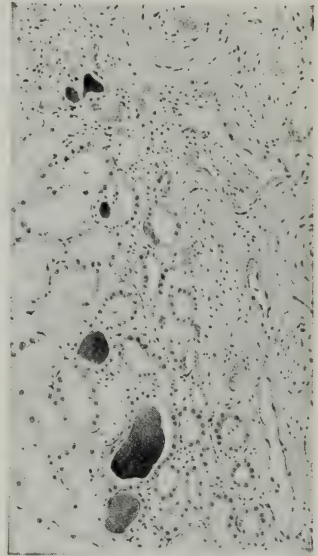


FIG. 22—Hyaline casts in lumina of renal tubules.

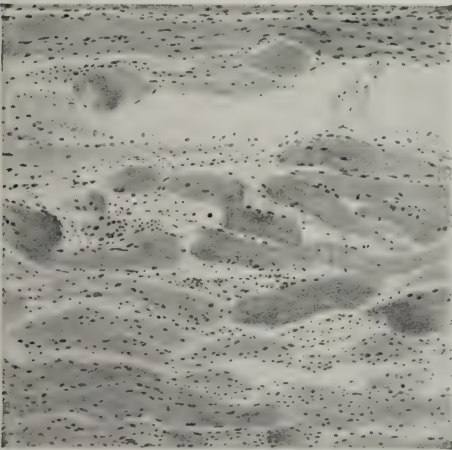


FIG. 23—Zenker's hyalin of voluntary muscle and reaction in fixed tissues.

transverse striation, the muscle substance is clear, translucent, homogeneous and takes the acid stain. The softening of the muscle often gives the fiber a somewhat wavy appearance and between the fractured ends of the hyaline material the space is bridged by the muscle sheath. The muscle nuclei are usually completely absent. Wells ascribes the change to increased accumulation of acid, the result of deficient oxygen supply. Since muscle has a very low power of regeneration, repair is by the formation of scar tissue. The change differs from several of those

indicated above in that it represents complete death of the muscle bundles affected, whereas many of the changes mentioned above represent simply retrogressive changes from which the tissues may recover.

Mucinous Degeneration.—The gross characters of mucin are familiar in the structureless, clear, viscid material secreted from the nose and throat. Because of these gross characters the material is included among the hyalins. Microscopically, however, the character depends largely upon precipitation by the fixing agent. At times mucin appears under the microscope as a finely granular material and again as a clear structureless hyaline material. It can be differentiated from other forms of hyalin by virtue of the fact that it takes the basic dyes. It is soluble in weak solutions of alkali and is precipitated by

weak acids, particularly acetic acid.

By virtue of the fact that it contains a sugar it will reduce Fehling's solution after having been boiled with strong acid. The presence of a small amount of sulphuric acid is probably the reason for the fact that mucin takes basic dyes. In man and in other mammalia, mucin may be produced either by epithelium or by connective tissue cells. The normal prototype of that secreted by epithelial cells is seen in mucus from epithelial glands. The normal prototype of connective tissue mucin is seen in that of the umbilical cord. Following Cohnheim's suggestion the former is referred to as mucin and the latter as mucoid.

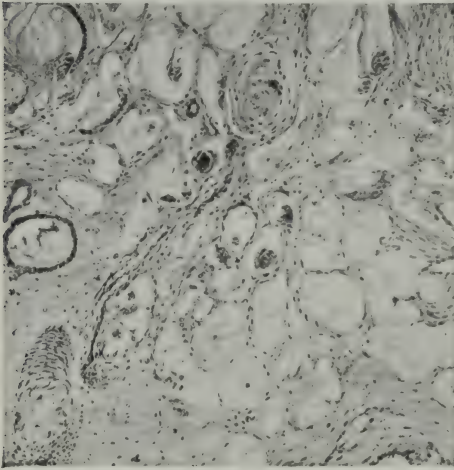


FIG. 24—Mucinous degeneration in carcinoma of rectum. Large spaces are filled with mucus, sometimes with preservation of gland cells, sometimes with desquamated centrally disposed cells and sometimes with disappearance of cells.

Wells describes mucin as a "compound protein consisting of a protein radical and a conjugated sulphuric acid which contains a nitrogenous sugar." Analysis shows slight differences in the composition of mucins from various origins and in a general way the mucins contain less sulphur than the mucoids. Levene found that certain of the connective tissue mucoids contain chondroitin-sulphuric acid and that others, including true mucins, contain mucoitin-sulphuric acid. The former group includes the mucoid of cartilage, tendons, aorta and sclera; the latter includes gastric mucin, Wharton's jelly, vitreous humor, cornea and ovarian cysts. The protein of the mucin or mucoid serves as an antigen in the immunological sense, and the reactions indicate a close similarity of the protein of epithelial mucin and of connective tissue mucoid.

The term mucinous degeneration refers to the formation of an excess of mucus with an associated degeneration of the epithelial cells. It is often difficult to be certain that cells are the seat of mucinous degeneration rather than simply the seat of an excess of mucin formation. For example, the cells of the large intestine and of the appendix often show typical goblet forms under normal circumstances. The diagnosis of mucinous degeneration in this situation de-

depends upon the determination of an excess of mucin production in association with degenerative changes in the cells, more particularly cloudy swelling. In confined situations such as cysts, it is easily possible to determine an excessive production of mucin by the distension of the cyst. The condition is frequently seen in catarrhal inflammation of mucous membranes. It is also well exemplified in certain tumors of epithelial origin, formerly called colloid cancers but more properly designated as mucinous cancers. In these tumors the epithelial cells form acini and secrete considerable quantities of mucin. Secondary to the distention of the acini by the excess of mucin, the cells undergo cloudy swelling and atrophy.

Connective tissue mucoid is present normally in the intercellular tissues. Pathologically, this may be increased in myxedema, a curious thickening and swelling of the skin seen in connection with deficiency of thyroid secretion. It is also found in myxoma and various combinations of myxoma with other tumors. Here it resembles the mucoid of the umbilical cord. The cells of the tumor are of stellate and spindle shape with interlacing processes, between which the basic stained mucoid lies. A somewhat similar histologic appearance is given by edema of certain fibrous tumors, particularly nasal polyps. The edematous material between the cells in these cases takes the acid stain faintly, whereas if mucoid be present the material takes the basic stain faintly. Not infrequently mucoid may be found during the process of arteriosclerosis lying between connective tissue cells and processes, of the intima of the aorta and other large vessels.

Pseudomucin.—Within the cysts of the simple multiple cystic ovary is sometimes found a pale yellow, clear, translucent, viscid, semi-solid or gelatinous material which is called pseudomucin. In the softer or fluid forms it resembles very closely epithelial mucin. Although on boiling with acids it will reduce Fehling's solution as does mucin, yet it is alkaline in reaction and is not precipitated by acetic acid. Histologically it is clear, homogeneous and structureless, and in contrast to true mucin takes the acid stain. Similar material is found in some of the cysts of the congenital cystic kidney as well as occasionally in other cysts.

Colloid Degeneration.—The term colloid was originally employed to indicate a clear, gelatinous, brown, hyaline material, similar in gross appearance to the colloid of the thyroid gland. With more careful study of the colloid of thyroid gland, it was found that this substance differs chemically from other hyaline materials which have essentially the same gross appearance. Considerable confusion in the employment of this term has resulted and it is considered advisable to restrict it to a material essentially the same as that secreted by the thyroid. The other substances of similar gross appearance may be called hyalin, or if it be considered desirable to indicate the naked eye appearance, they may be referred to as pseudocolloid. True colloid has its

normal prototype in the thyroid gland. The material secreted by the thyroid epithelium is at first an albuminous fluid, but subsequently, either by inspissation or by the additional secretion of other substance, becomes a clear hyaline material. In the normal thyroid this material appears perfectly hyaline under the microscope, takes the acid stain, occasionally shows a scalloping of the edges next to the cells and frequently, because of its density, shows a certain amount of marking by the section knife. In the condition known as colloid goiter the amount of colloid is materially increased and the acini may attain large size. Sometimes the acinus may increase in size so as to become visible to the eye as a cyst. In cancers and other tumors of the thyroid the colloid may be increased, and the metastases of thyroid cancers frequently show material which is identical. It was formerly supposed that the hyaline material seen in the anterior lobe of the hypophysis is similar to but not identical with the colloid of the thyroid gland, but Wells maintains that only when

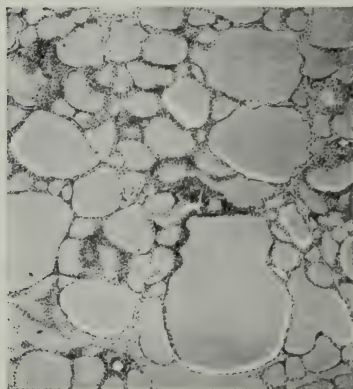


FIG. 25—Colloid degeneration in adenoma of thyroid gland.

iodin is given therapeutically does it appear in the hypophyseal colloid. The particular material characteristic of colloid is iodin, which appears in the form of an iodin containing protein or iodin-protein combination called thyro-iodin. Further refinement of examination shows this to be a thyreoglobulin. The activity of thyroid substance depends upon the presence of iodin in some such combination. Kendall has isolated a crystalline substance which is called thyroxin, apparently a product of iodin and indole, the formula representing a thyro-oxyindole. This is said to have all the pharmacological activity of thyroid gland.

Hyaline substances resembling colloid grossly may appear under a variety of circumstances. Usually, this pseudocolloid is formed by an inspissation or condensation of some other material. In the kidney, for example, it is not uncommon to find cystic dilations of the tubules which contain a brown gelatinous material. Histologically, this takes the acid stain somewhat less deeply than do the simple hyaline casts. The same material may be found in the congenital cystic kidney which is a defect of development whereby the kidney is made up largely of numerous cysts containing either pseudocolloid, hyalin, or thin, serous fluid. The pseudomucin of the ovary may also become condensed after a long time and give the gross appearance of pseudocolloid. Numerous other conditions where cysts are formed may lead to the same appearance. This may be true regardless of whether the cysts contain old blood, old serum or old protein material of almost any nature. These substances then apparently represent a condensation of protein material not containing iodin and therefore differentiated sharply from true colloid. Histologically, practically all these materials take the acid stain and show an entirely structureless hyaline character.

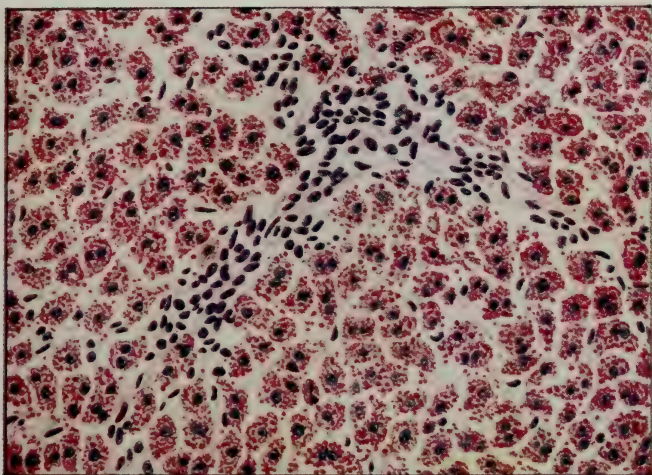


PLATE III—Glycogen infiltration in liver of rabbit, stained by the Best carmine method and counterstained with hematoxylin.

Glycogen Infiltration.—Glycogen appears in tissues as a hyaline substance with particular staining reactions and with a definite composition. It is the only one of the carbohydrates which can be demonstrated microscopically. It appears in the form of a labile or depot glycogen in the liver and in muscle. The amount in these situations varies with work performed and nutrition supplied. Whether glycogen appears in the cells only in pure form or whether it exists in combination with some other substance is an open question. The fact that microscopically the droplets of glycogen are often found in close approximation to, or in combination with, the cell granules, leads to the supposition that perhaps there is combination between glycogen and protein. Even if this be true, it seems not to interfere with the lability of the substance or with its staining reactions. In contrast is the stabile form of glycogen which may appear in almost any tissue and is particularly evident in those tissues which are somewhat removed from direct contact with the blood stream, such as cartilage and the upper layers of cutaneous epithelium. Practically any cell in the body may contain glycogen although it may not be demonstrable microscopically. Glycogen is likely to appear in many places which also show fat, and it is probable that essentially the same causes influence the appearance of both these substances. Glycogen is, however, much more labile than fat and disappears more readily. Studies of glycogen in skeletal muscle show a reduction after work and Richard's study indicates that the same is true of smooth muscle. The curve of disappearance of glycogen shows an abrupt fall after death of the cells or of the body, but in the course of eight or ten hours the decline is more gradual. Whether the ferment concerned in glycogenesis and in glycolysis is the same or not, is of little importance in the present connection, but certainly is of significance in general disturbances of carbohydrate metabolism. The rapidity of glycolysis after death is so great, however, as to demand immediate fixation of tissues in some substance in which glycogen is not soluble. For this purpose strong alcohol or watery fixatives saturated with dextrose are employed. After such fixation the tissues may be embedded in paraffin or celloidin and subsequently stained. The simplest stain is iodine which imparts a brown color to the glycogen. This, of course, resembles the reaction of amyloid but can be differentiated by virtue of the fact that the glycogen even after fixation is soluble in ptyalin or saliva. An excellent method of demonstrating glycogen is the Best carmine stain, which gives a brilliant red color to the droplets of glycogen. If watery fixatives be employed the glycogen is dissolved, and when stains are applied to such tissues the presence of glycogen is only indicated by vacuoles in the cells. Study of the specially fixed and stained preparation shows the glycogen as small or large droplets of perfectly clear homogeneous structure. For the most part these droplets are in the cytoplasm, but occasionally they may appear in the nucleus under which circumstances the nucleus usually is somewhat vesiculated.

Pathologically, glycogen may appear in a variety of situations. In any case it is entirely in the nature of an infiltration, apparently does no damage to the cells, and may disappear readily. Glycogen is likely to appear in the cells of

that reactive inflammation which appears about local areas of dead tissue, where it is very commonly associated with fat. If fixation be delayed, the glycogen may readily disappear and lead to the inference that only fat is present. Other localized chronic inflammations may show the same process. The cells which take part in acute inflammation, particularly the leucocytes, are likely to show iodophilic droplets of glycogen in the cytoplasm. Not only is this true of leucocytes involved locally, but those in the circulating blood similarly show iodophilic granules. This character of the cytoplasm of leucocytes is not necessarily pathological and the presence of such cells in circulating blood has been proved after long study to have little or no diagnostic significance. Embryonic and fetal cells are likely to be richer in glycogen than are adult cells. Consequently it was presumed that those tumors which more nearly approach the embryonic type of cell growth are likely to show a greater content of glycogen than are other tumors. This generalization, however, is not justified in its entirety, since local degenerative changes in the tissues may alter very materially the content of glycogen. The studies of Lubarsch indicate that the simpler connective tissue tumors of benign character are likely to show little or no glycogen. The exceptions to this rule appear in the chondroma and myoma. The adenoma is likely also to be free from glycogen. Malignant tumors of both connective tissue and epithelial origin are likely to show considerable amounts of glycogen. This, however, can have no diagnostic significance because in an analysis of the figures only about half the malignant tumors show glycogen. Lubarsch reports that glycogen is constant in teratoma, rhabdomyoma, hypernephroma and chorionepithelioma.

In diabetes the glycogen is more or less exhausted from the ordinary depots such as the liver and muscles. Nevertheless, tissues which do not ordinarily contain much glycogen are likely to show it in considerable amounts. It may be found in heart muscle, in leucocytes, in capillaries of the brain and in the tissues of the eye. Of particular importance, however, is its presence in the kidney. This situation is fairly common in human diabetes and is also found in experimental diabetes caused by excision of the pancreas and by puncture of the floor of the fourth ventricle. It is seen particularly well in the cells of the loops of Henle, either in the form of numerous small globules or as larger masses which may exceed the size of the nucleus. The presence of large vacuoles in these particular cells, when special methods have not been employed, is almost diagnostic of glycogenic infiltration. With the special stain the appearance is striking. Recent studies indicate that the epithelium of the convoluted tubules exhibits the glycogen more commonly than the loops of Henle. Studies of Löschke show that the glycogen is synthesized in the epithelium of the capillary loops of the golmeruli, passes into the urine and is reabsorbed in the convoluted tubules. Perhaps subsequent reabsorption occurs in the cells of Henle's loops. Klestadt suggests that the excretion of large quantities of sugar in the urine, rather than the disease complex diabetes, determines the appearance of glycogen in the kidney. Klestadt's review of the literature would indicate that the loops of Henle are more frequently involved in human diabetes

than are the convoluted tubules. The reason for the accumulation of glycogen in cells other than those of the glycogen depots and particularly in the cells of the kidney remains as yet unexplained.

Gierke states in summary that the content of glycogen in the cells is dependent upon the type of cell, the state of nutrition and the nature of the injury.

Amyloid.—Amyloid is distinguished from the other hyalins in that it is somewhat more glassy on gross inspection, and especially because it stains in a specific manner with iodine, iodine and sulphuric acid, and aniline stains particularly, methyl violet, aniline gentian violet and methyl green. It is likely to affect the spleen, liver and kidney, and in addition, quite commonly also the adrenals, stomach, heart; in some instances it may be widely generalized throughout the body. Occasionally, it may be found affecting the whole or only a small part of a single organ. The most common cause of the disease is chronic suppuration, particularly that secondary to and implanted upon tuberculosis. It may, however, be seen in non-suppurative forms of tuberculosis, in syphilis, both the acquired and congenital forms, and secondary to tumor formation in the body with or without ulceration, and occasionally is seen without any of these causes. Amyloid may occur in association with chronic nephritis, cirrhosis of the liver and other chronic non-suppurative diseases, but to what extent these diseases serve as a cause for amyloid formation is still a problem.

Microscopically, amyloid is found to affect the smaller blood vessels, although it may occasionally be seen in the aorta and in the endocardium of the heart. In capillaries the amyloid is deposited immediately outside the endothelial lining as a hyaline mass (see Ohmori). In slightly larger vessels, it occurs in the connective tissue immediately outside the endothelium, whereas in arterioles and venules of medium size, it is found between the muscle cells of the media. It has never been found within cells except in those rare instances where the process leads to tissue reaction and the formation of multinucleated giant cells which may ingest small particles of amyloid by the process of phagocytosis. In many situations it is difficult to distinguish between amyloid and other forms of hyalin. It is usually necessary, therefore, to apply some of the specific stains. The simplest of these is iodine in the form of a watery solution such as Lugol's solution, which imparts to the amyloid a deep brown color. This reaction can be distinguished from that of glycogen only by the position of the hyaline material, since glycogen is almost always intracellular. After treatment with Lugol's solution, dilute sulphuric acid may be applied which changes the color from the deep brown to a reddish-brown, brownish-

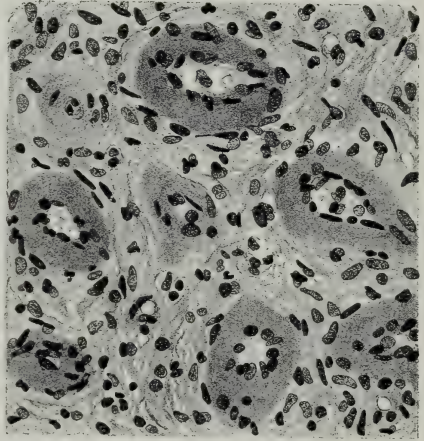


FIG. 26—Amyloid in walls of splenic sinuses.

blue or blue-black. This reaction is usually clear cut and is specific, but in certain cases of amyloid does not appear. The most specific of these reactions is the methyl violet reaction. Of equal value is the use of aniline gentian violet, methyl green or some of the other metachromatic aniline stains. With these stains the tissues take the blue, green or other color of the stain and the amyloid is stained red or some shade of red. The deposit of amyloid leads to alteration of the cells of the tissue for two reasons; it may be deposited in sufficient amount to produce pressure upon surrounding cells and thereby lead to atrophy of these cells, or the amount of amyloid may be so great as definitely to limit the internal calibre of the affected blood vessels, thereby leading to cloudy swelling and fatty degeneration and atrophy or necrosis, because of the limitation of nutrition. Cellular atrophy is best seen in the liver, whereas the nutritional changes, such as fatty degeneration and cloudy swelling, are best seen in the kidney. In the spleen the amyloid is found first in the media of the central arteriole of the follicles. Subsequently, it appears in the follicles as a network made up of very coarse fibers which finally collect to form a solid mass of amyloid. Still later it extends out through the pulp of the spleen, usually along the walls of the splenic sinuses. In the kidney, the change is seen first in the capillary loops of the glomerular tufts. It is also likely to be found in the walls of the arteriæ rectæ of the pyramids and, to a less extent, in the interlobular arterioles of the cortex. In advanced cases, amyloid may be found lying under the epithelial cells of the tubule, involving the basement membrane. In the liver, amyloid in most cases affects primarily small arteries and veins of the capsule of Glisson. It is likely to be most extensive, however, in the sinusoids of the lobules. Here it appears immediately outside the endothelium of the sinusoids, particularly in the middle part of the lobule. As it becomes more extensive the central and peripheral parts of the lobule also are affected. As the condition advances the pressure atrophy of the liver cells becomes more and more marked and amyloid from adjacent sinusoids may fuse to form a solid mass of considerable size. Amyloid of the heart is most likely to be found in the subendothelial connective tissue of the endocardium of the right atrium. It may occasionally be found in the capillaries of the myocardium of the ventricular walls. It affects the intestine particularly in the muscular coat, but occasionally may be found very sharply defined in the capillary loops of the villi. In the adrenals it appears particularly in the capillaries of the cortex and may attain such dimensions as to produce pressure atrophy of the cortical cells.

Grossly, organs the seat of amyloid disease are usually considerably enlarged, firm, show a tense capsule and a rounding of any sharp edges. Both on the outer surface and on the cut surface the organ is pale, due principally to the limitation of blood supply brought about by the extent of the amyloid process. The organ cuts with slightly increased resistance and shows a cut surface which neither bulges nor retracts unless other changes are present. It is a firm, non-friable cut surface showing in the more extensive cases a generalized glassy appearance. In certain instances, which will be mentioned, amyloid may appear as small points of glassy translucent material which transmit the color of the

underlying organ. When the process is extensive, the organ resembles somewhat fresh hog fat and therefore the term "lardaceous" has been applied. In the liver, the large, pale, firm organ may show in the cut surface irregularly distributed points of amyloid, which in association with hyperemia of the central zones may produce the appearance called "nutmeg amyloid liver." The spleen in this disease is large and firm, but is not more pallid than is normally the case. The earlier stages of amyloid, affecting the follicles, show to the naked eye numerous small areas of glassy material transmitting the red color of the spleen. These small masses resemble boiled sago grains and the organ has been called the "sago spleen." In later stages the spleen may be diffusely

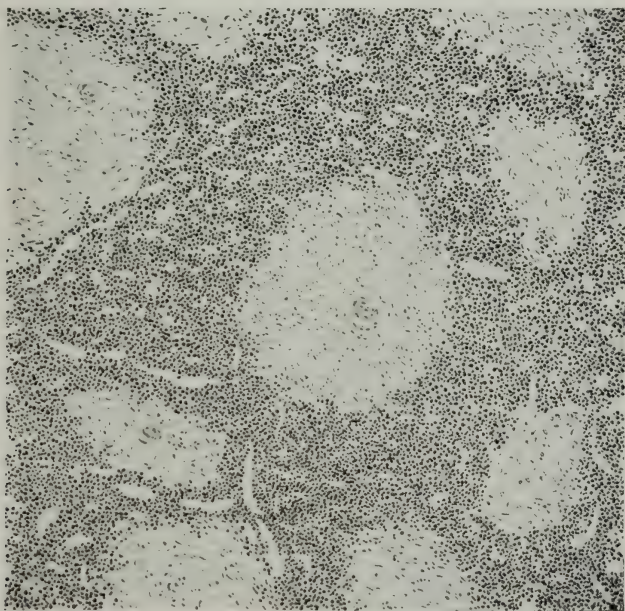


FIG. 27—Amyloid in splenic follicles, the histologic picture of the sago spleen.

involved and become the "lardaceous spleen." The kidney of amyloid is a large, pale, firm kidney which to ordinary inspection shows nothing characteristic of the amyloid. In any of these instances it is customary to apply gross staining in order to make the diagnosis of amyloid. Usually this is done by the application of Lugol's solution. If the organ be very bloody, it is well to wash with dilute acetic acid so as to remove most of the blood before applying the Lugol's solution. The amyloid under these circumstances takes the iodine stain in the form of deep reddish-brown color (mahogany brown). In the liver and spleen this can be seen very readily. In the kidney, however, it requires close inspection to make out the amyloid deposit in the glomeruli. In doubtful cases it is sometimes necessary to apply in addition dilute sulphuric acid, whereupon the changes mentioned above appear, namely, a brownish-red, deep blue; or brownish-black color. Occasionally, amyloid is found which gives neither of

these reactions. In these instances it is usual to apply the methyl violet reaction to frozen sections, although the same reaction can be preformed with the gross cut surface. It can be stained intravitaly by the use of Congo red or trypan blue (Herzenberg).

Litten, in an analysis of 250 cases of amyloid disease, found various organs affected in the following percentages—spleen 99 per cent., kidney 98 per cent., endocardium 76 per cent., liver 65 per cent., intestinal mucosa 67 per cent.

The Nature of Amyloid.—Virchow, in 1853, applied the name amyloid (starch like) because this substance gives a blue color when treated with iodine and sulphuric acid. A few years later it was demonstrated that the material is protein in nature, since it responds to the xanthoproteic reaction. Oddi, in 1894, and Krakow, in 1897, found that amyloid organs contain considerable quantities of chondroitin-sulphuric acid and assumed that amyloid is a compound of protein and sulphuric acid similar in general composition to nucleoprotein which contains protein and nucleic acid. Hanssen, however, in 1908, isolated amyloid from the spleen and failed to find chondroitin-sulphuric acid, although the spleen tissue contained sulphur as sulphate in considerably increased quantity as compared with normal spleen. Similar increases were found in the liver but less marked in the kidney. He concluded that although chondroitin-sulphuric acid is not a component of amyloid, yet the same cause which leads to the increase of this acid in the tissues, leads also to the deposit of amyloid. This report has not been confirmed save for a passing remark of Mayeda. It is supported by most painstaking work and should be tentatively accepted. Further support is offered by the fact that experimental attempts to produce amyloid by the use of chondroitin-sulphuric acid have failed. Amyloid takes acid stains and is therefore basic in character. Kuczynski claims to have produced amyloid in mice by feeding a rich protein diet. He found the amyloid rich in tyrosin and the crystalline form of amyloid almost identical with tyrosin. Neuberg analyzed the protein of several amyloids and found it rich in diaminonitrogen, which probably accounts for its basic character. If conjugated sulphuric acid be present, it is in such small amounts as not to influence the basic reaction. Although chondroitin-sulphuric acid is present normally in cartilage and elastic tissue, yet elastin differs materially in composition from amyloid. A fairly close relation in composition is found between amyloid protein and gelatin although the latter contains considerably more monamino-acid nitrogen. Neuberg regards amyloid protein as a simple protein, the result of transformation of the tissue protein. This conforms to the fact that amyloid is seen especially in those diseases where there is much destruction of tissues. Leupold reports a positive Abderhalden reaction between amyloid as substrate and the blood serum of victims of chronic suppuration. The ferment responsible is supposed to be elaborated in the body in response to the presence of the specific protein, which is subsequently transformed into amyloid. The exact application of this phenomenon is not clear, but it is interpreted as indicating that the colloid protein, precursor of amyloid, circulates in a disperse phase to be precipitated by other agents.

Numerous attempts have been made to produce amyloid experimentally in animals. Repeated failure has followed the use of chondroitin-sulphuric acid, either isolated and used pure or as a sodium salt, or in the form of cartilage and mucin. The feeding of flowers of sulphur was also ineffective. The same is true of nucleoprotein of pus, and of Witte's peptone. The production of long continued suppuration by bacteria such as *staphylococcus pyogenes aureus*, or by the use of oil of turpentine has led to the formation of amyloid in experimental animals. Suppuration, however, is not essential, since the intravenous injection of bacteria not leading to pus formation, as well as the injection of bacterial toxins may be followed by the formation of amyloid.

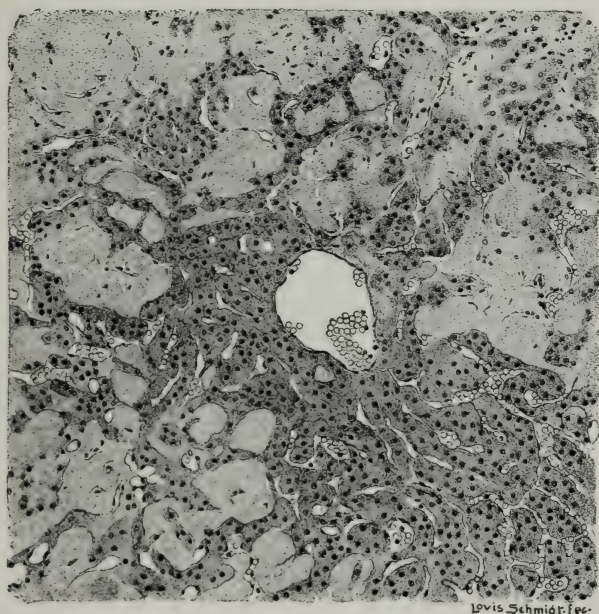


FIG. 28—Amyloid of liver, showing amyloid between atrophic cell cords.

This, however, requires repeated injections and we have failed to confirm Domagk's statement that amyloid can be produced within a few minutes after injections of dead and living bacteria. It is stated that injection of sterile pus and of certain ferments may lead to amyloid deposit. Apparently the most favorable organism is the *staphylococcus*. Hirose, however, was entirely unsuccessful in a large series of experiments with this organism, but Bailey was successful in all his animals which survived repeated intravenous injections of *bacillus coli communior* over eighty-eight days or more. The best results have been obtained with the rabbit, dog, mouse, horse and hen. Davidsohn reports positive results in one-third of one hundred rabbits injected with *staphylococcus pyogenes aureus*, but most other investigators have been less successful. Davidsohn reports a complete failure to produce amyloid in rabbits whose spleen had been removed. Kuczynski, however, produced it in splenectomized mice.

The use of turpentine and of various other sterile substances is in several instances open to the question, as to whether or not infection and tissue destruction have accompanied the treatment. Nevertheless, it is apparent in the use of bacteria intravenously and of toxins, that such tissue destruction does not necessarily occur and yet amyloid supervenes.

Leupold claims to have produced an iodophilic hyalin by treatment of excised spleen tissue with dilute sulphuric acid, but this failed to respond to the iodine-sulphuric acid or methyl violet reactions. That such a hyalin could subsequently be transformed into amyloid is open to great question, although it must be admitted that the reverse is probably true, namely that deteriorative changes in amyloid may result in the formation of a hyalin without specific reactions. With the exception of Bailey's experiments, the production of

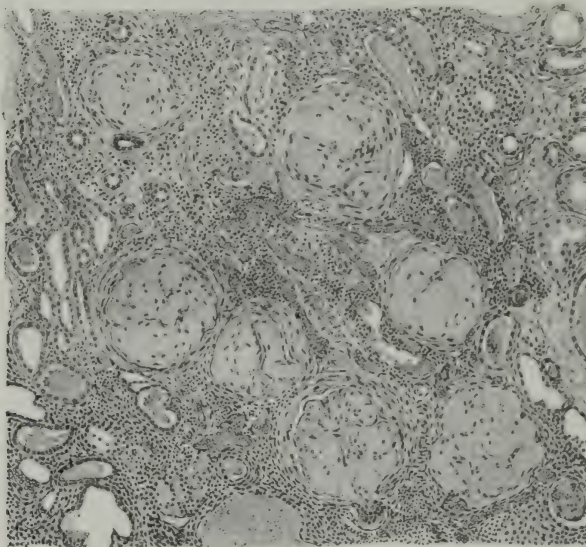


FIG. 29—Amyloid in capillary tufts of renal glomeruli.

amyloid in animals has been extremely variable. Essentially, then, amyloid is known to be a protein complex but is to be differentiated chiefly by its staining properties.

The Mode of Deposit of Amyloid.—Numerous hypotheses have been offered as to the mode of deposit of amyloid but none is completely satisfying. The academic question as to whether it is an infiltration or a degeneration remains unanswered. Czerny thought that it results from the deposition of iodophilic granules of leucocytes but no convincing evidence is offered. Browicz found amyloid nodules in the lumina of veins and offered the theory that amyloid represents a coalescence of erythrocytes. The usual position of amyloid fails to support this idea, and M. B. Schmidt believes that the amyloid within veins is in that position because of rupture of the vein walls. With the discovery of chondroitin-sulphuric acid in amyloid organs, it was suggested that this substance circulates in the blood as the result of destruction of cartilage in

tuberculosis of joints or of other structures which contain elastic tissue, and that in the organ to be affected by amyloid there is a combination with intercellular protein, such as the cement substance, to form amyloid. This theory must be abandoned with the acceptance of Hanssen's statement that chondroitin-sulphuric acid does not appear in amyloid. M. B. Schmidt thinks that the formation of amyloid is closely connected with antibody formation, since it is seen in diphtheria antitoxin horses and following repeated bacterial injections. This, however, would not explain its presence following turpentine injections or in cancer patients. Fundamentally, according to Schmidt, there occurs a sort of coagulation of special protein by the activity of a ferment. Davidsohn, because of failure to produce amyloid in splenectomized rabbits and because the spleen is more frequently affected than any other organ, believes that the spleen elaborates the ferment concerned, but as stated above, it occurs in splenectomized mice. Leupold supposes that suppuration, or other destructive processes, leads to the formation of a protein precursor of amyloid which appears in the blood plasma and other fluids as an emulsion colloid. Coming into contact with an abnormally rich amount of conjugated sulphuric acid in certain organs, the protein is precipitated to the gel state and constitutes the amyloid. By previous active oxidization of amyloid by the use of potassium permanganate he was able to dissolve the amyloid in acids and bases, thus establishing in his opinion the reversibility of the reaction. According to J. Loeb's experiments with gelatin, acid precipitation involves combination of the acid with the protein, but this is apparently not true in the formation of amyloid. Furthermore, acid in order to operate as a precipitating agent for colloids must be ionized. Presumably the sulphuric acid if present, is in organic form and would not be ionizable. It will be seen that no hypothesis concerning the mode of deposit of amyloid can be accepted without further knowledge of the chemistry of this substance.

Local Amyloid Deposits.—In contrast to the usual involvement by amyloid of several or many organs, occasional cases of amyloid in restricted areas are reported. This is quite aside from those early cases of amyloid disease in which the spleen alone is affected, since this represents undoubtedly the earliest stage of a general amyloidosis. The same may be true in cases of involvement of lymph nodes draining tuberculous and chronic suppurative foci. Small swellings containing amyloid, sometimes called amyloid tumors, have been reported at the base of the tongue, in the mucosa of the larynx, trachea, and bronchi, as well as in that of the nasal septum. The amyloid in these instances is usually found in the lymph vascular system but may be seen in the blood vessels and in the tissues. The fact that these situations are in close relation to cartilage offers a suggestion as to the reason for a local concentration of chondroitin-sulphuric acid, whether this acid combines with proteins or merely serves to precipitate them. The presence of elastic tissue offers a similar suggestion in regard to deposits solely in the heart. Much less clear are the cases of amyloid in the wall of the urinary bladder and occasionally in tumors of endothelial origin.

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CHAPTER IV

NECROSIS AND SOMATIC DEATH

INTRODUCTION.

SOMATIC DEATH.

SIGNS OF SOMATIC DEATH.

CESSATION OF CIRCULATION AND RESPIRATION.

ALGOR MORTIS.

RIGOR MORTIS.

LIVOR MORTIS.

POSTMORTEM CLOTTING.

DESICCATION.

PUTREFACTION.

AUTOLYSIS.

MORPHOLOGICAL CHANGES IN DEATH.

NECROSIS.

ETIOLOGY.

MORPHOLOGY.

TYPES OF NECROSIS.

COAGULATION NECROSIS.

CASEOUS NECROSIS.

LIQUEFACTION.

FAT NECROSIS.

LIVER NECROSES.

GANGRENE.

GAS GANGRENE.

Introduction.—Death signifies the complete cessation of functional and metabolic activities of the cell. In unicellular organisms death does not naturally occur because these bodies divide to form two or sometimes more new individuals from the original cell. Such reproduction does not leave as a product the dead body of any predecessor. As a group, such organisms may then be regarded as immortal. Accidents of various kinds may kill certain individuals or groups of individuals, but the main stem goes on uninterrupted. In addition, life may be preserved in the form of spores of bacteria, and fungi and seeds of plants, without any apparent metabolic activity. In multicellular organisms, reproduction depends upon the activity of a germ plasm. The germ plasm may be regarded as immortal in the same sense as are unicellular organisms. Each germ cell is the decendent of a previous germ cell and represents the ancestral strain, although during each generation its multiplication gives rise to the somatic cells of the individual. It is therefore essential in the consideration of death to differentiate between germ plasm and somatoplasm. The latter constitutes the body of the multicellular organism. Applying this principle to man it is seen that the family line is represented by the germ plasm and the individual members of the family represented by the somatoplasm. In multicellular organisms, it is possible to differentiate between three forms of death. *Somatic death* indicates death of the entire organism. *Necrobiosis* signifies death of certain groups of cells and replacement by new cells in the normal course of bodily activity. This is seen particularly in the skin of man where the desquamating superficial epithelium dies, is cast off and is replaced by new cells arising from the lower layers. It seems certain that essentially the same

process goes on in connection with practically all the cells of the body with the exception of highly differentiated cells such as those of the central nervous system. The third form of death in the body is referred to as necrosis. *Necrosis* indicates death of a group of cells or a localized part of an organ or tissue in connection with a living body.

Somatic Death.—In normal life all the organs and tissues of the body co-operate in the preservation of life. Certain organs and tissues, however, are absolutely essential. These include the respiratory system, the cardiovascular system, and the central nervous system. Complete failure of function of any of these systems leads to death of the entire organism. Fundamentally, of course, the immediate cause of death is failure of circulation, because upon this function depend all the other activities of the body. Failure of the central nervous system not only leads to deficient coördination of various bodily functions, but results in death because of removal of those stimuli which lead to cardiac and respiratory activity. Failure of the respiratory system removes from the body the entire respiratory function upon which oxidation and removal of carbon dioxide depend. With any of these functions removed, therefore, death must ensue. Certain organs, particularly the liver, the kidney, and certain glands of internal secretion, are essential for the preservation of life. The removal of these organs does not necessarily lead to immediate death. Death in certain instances is referred to insufficient internal secretions which in various ways are responsible for coördination and activation of metabolic and other functional activities. In just what degree the kidneys and liver contribute internal secretion is not at the present time known, but there is little support for any assumption that they operate other than as glands of external secretion and organs important in metabolism. Dogs usually live about four days after the removal of the kidneys. In human cases where, by accident a solitary kidney is removed, with congenital absence of its fellow, or the same condition is attained by ligation of both ureters, death may not intervene for a week or more. Cases are reported in which the liver in man has been removed where it has been so altered by disease as to be mistaken for a tumor. The work of Mann and his collaborators shows that in dogs the liver may be removed and the animal survive for several days provided an adequate supply of glucose is maintained in the blood.

Signs of Somatic Death. Cessation of Circulation and Respiration.—The diagnosis of death in man depends upon the demonstration of cessation of cardiac and respiratory activity. Cessation of cardiac activity may be demonstrated by absence of the pulse on palpation and by absence of heart sounds by auscultation. Cessation of respiration can usually be determined very readily, but in case of doubt, the absence of clouding of a mirror held close to the nose and mouth lends additional support to the diagnosis. Deep coma may sometimes closely simulate death, but only in the rarest instances is there reason for believing that ordinary means of diagnosis are insufficient to make the diagnosis. Remarkable cases of restoration of life after apparent death depend probably upon inadequate observation and insufficient study of the criteria

of death. Numerous tests are described in texts on legal medicine and can be found well described by Cattell. The secondary changes subsequent to somatic death appear within a very few hours and these leave no doubt as to the complete cessation of functional and metabolic activities. These secondary changes include algor mortis, rigor mortis, livor mortis, clotting of blood, putrefaction and decomposition.

Algor Mortis.—Cooling of the body occurs as the result of the gradual equalization of its temperature with that of the surrounding medium. It has been shown that a dead human body in the nude state, under ordinary circumstances cools at the rate of about 1° F. per hour. According to Brouardel, the temperature of the interior of the body, as indicated by rectal thermometer, equals that of the exterior in about forty hours after death. Extremely cold outside temperatures may hasten, and warm temperatures retard cooling of the body; a thick layer of fat may retard cooling. Occasionally death may be followed by a great increase in body temperature. This may occur following death from acute infectious disease, certain diseases of the nervous system, as well as death from certain other causes. This, however, is of short duration and probably depends upon active metabolism continuing after death without that element of radiation which depends upon circulation of the blood and body fluids.

Rigor mortis signifies the stiffening of muscles after death. It begins first in the involuntary muscles such as the heart. It usually affects the voluntary muscles within twelve hours after death, and usually passes off in three or four days. It is seen first in the muscles of the head, particularly the eyelids and the muscles of the jaw, and thence progresses to the muscles of the neck and downward over the body. Many times, however, the arms are involved last. As a rule, the flexors predominate over the extensors. The appearance of rigor is hastened by warm temperature and retarded by cold. Its disappearance is likely to be retarded by cold and hastened by heat. Metabolic activity at the time of death appears to play an important part in producing this condition. Accordingly, individuals who die from acute infectious fevers and those who are killed in the midst of great muscular activity are likely to show rigor mortis earlier than others. Heavily muscled individuals are likely to show early and pronounced rigor. Poisons such as strychnin and veratrum viride are likely to lead to marked rigor which may persist for a very long time. Ordinarily the rapid onset of rigor is followed by delayed disappearance. When rigor disappears from a corpse or when it is broken by force it does not return again. Although it was formerly supposed that rigor represents a sort of tetanic contraction of muscles, not differing from the physiological and probably dependent upon the removal of inhibition, at the present time there is no doubt that this condition represents a chemical change in the muscle. By vital staining it can be shown that in contraction of muscles during life there is no important histological change, whereas in rigor mortis there is a definite precipitation of protein. Two substances can be extracted from muscle, myosinogen and paramyosinogen, both of which are changed into insoluble myosin at low temperature. This coagulation, however, is not identical with blood clotting. Pro-

teins play a certain rôle but apparently the presence of acid is of the utmost importance. The normally amphoteric muscle becomes slightly acid when at work and the same is true when its circulation is occluded. This is due very largely to the formation of sarcolactic acid. The formation of myosin is probably a part of, or accompanied by, certain physical changes in the protein of the muscles. Wells states that the presence of the sarcolactic acid is sufficient to cause a swelling of the muscle colloid, which may be so great as to destroy the structure of the muscle cell and even be a cause of waxy degeneration or Zenker's hyalin. Collip finds that the point of maximal precipitation is between 6.3 and 6.6 index, which corresponds to the point at which muscle goes into rigor. Further acidification redissolves the precipitate. The swelling is due to the hydrophilic acid-protein and is reduced as the acidity is further increased, due to loss of hydrophilic property. Thus, as time goes on, the increasing acidity leads to loss of rigor. Neither postmortem decomposition nor autolysis is responsible primarily for loss of rigor.

Livor mortis is a red discoloration of dependent parts of the body due to sinking of the blood into these parts. It is seen in the form of diffuse or localized reddening in the dependent superficial parts, and as hyperemia in dependent organs or parts within the body. On cutting into such areas the blood escapes from the vessels in fluid form, in contradistinction to hemorrhage, in which, owing to the fact that the blood has clotted, it does not flow readily when the part is cut. Histologically, there is no difficulty in distinguishing between the simple hyperemia of livor mortis and the extravasation of blood in hemorrhage. If the position of the body be changed, the blood will slowly flow out from the old into the newly dependent parts. After death the blood corpuscles are dissolved with varying degrees of rapidity so that finally hemoglobin is found in solution in the blood serum. This material diffuses readily through, and visibly stains, the lighter colored tissues. This is particularly true of heart valves, and the lining of great vessels and of the larger serous cavities. Hemolysis and diffusion of hemoglobin are hastened particularly in death from infectious diseases, more especially when infection is due to hemolytic bacteria. The change is seen very strikingly in death from gas gangrene. There is, however, little reason for believing that such staining of tissues by hemoglobin occurs before death. For all practical purposes it is to be looked upon as a postmortem change.

Postmortem clotting of the blood appears very early. In cases of slow death, clotting may probably begin before death actually occurs; under these circumstances the clots are referred to as agonal. The postmortem clot is most commonly of the type called cruor clot or "currant jelly" clot, in which all the blood elements are coagulated in one mass; this type of clot has a characteristic, bright red color and jelly-like consistence. In cases of slow death and under other circumstances where the clotting does not proceed very rapidly, the red blood cells sink to the lower part of the clot and the leucocytes, because of their lower specific gravity accumulate in the upper part as a yellow, translucent mass. This is particularly well seen in the heart where the upper layer

of clot, namely, that nearest the anterior chest wall, is likely to be fairly firm and of light yellow color. The consistency and color give it the name "chicken fat" clot. Some cases of rather slow death show a whipping out of fibrin by the chordæ tendineæ of the heart which produces a firm, somewhat friable, white fibrin clot. Postmortem clotting and agonal clotting differ from antemortem clotting in a variety of ways, but it is particularly to be noticed that postmortem clot is not adherent to vessel walls. Sometimes the clot may, however, be rather firmly formed about the chordæ tendineæ and papillary muscles of the heart. In these instances, it can readily be seen, however, that this is simply due to clot formation and not the result of adhesion to the heart wall. In the vessels the distinction is very readily made, but there may occasionally be confusion because of the difficulty in withdrawing long clots from smaller branches of blood vessels. The differentiation is more fully considered in the discussion of thrombosis.

Desiccation of certain parts of the body is very common after death. This is particularly true in the cornea of the eye and the fluid of the anterior chamber. The cornea becomes dry, glazed, and because of sinking of the fluid into the rear of the eye, becomes wrinkled. Similar dryness of surfaces may be seen over wounds and abrasions or in other situations where the skin has disappeared or is extremely thin. Only rarely is drying of the tissues seen in the internal parts of the body. Occasionally, however, in marked emphysema of the lung, the lung itself may be dry and the dryness may be noticed in adjacent parts of the pericardium.

Putrefaction of the dead body is due to the entrance into the tissues of the rapidly multiplying saprophytic organisms of the intestinal canal. The growth of these organisms results in softening and putrefaction of tissues and the formation of numerous gases, particularly the offensive hydrogen sulphide. As has been pointed out in the chapter on pigmentation, these gases may alter body pigments so as to produce various color changes. The most prominent of these colors is the green discoloration which appears over the abdomen, due to interaction of hydrogen sulphide with the iron of blood and other tissue to form the greenish-blue iron sulphide. As has been said above, methemoglobin may be formed by the action of hydrogen sulphide; hematin may appear and other pigments are occasionally encountered. Putrefaction is retarded by cold and accelerated by warmth. It is also retarded by the use of chemicals such as formalin and arsenic. If obligate or facultative saprophytes gain access to the blood stream before death, decomposition is likely to proceed with great rapidity. This is seen particularly well in cases of gas gangrene. Gas formation in connection with decomposition of this sort is very rich and organs, particularly the liver, may become actually foamy because of the presence of bubbles of gas in the tissue. The presence of such foamy organs is practically diagnostic of the presence of the organisms of gas gangrene, and can be produced very readily by injecting a culture into a living animal, killing the animal and placing it for a few hours in an incubator.

Ferments. Autolysis.—Digestive glands secrete ferments which during

life produce decomposition of food products and after death are likely to digest the organs themselves. This is especially well seen in the stomach where, if the body be examined a sufficiently long time after death, or if conditions of warmth be such that digestion may proceed actively, the lining mucosa of the stomach or even the entire wall shows softening and disintegration. The same may be true, but to a lesser extent, in the small intestine. The pancreas frequently shows marked digestion. *Autolysis* is that process whereby tissues undergo digestion without the presence of bacteria or of ferments introduced from without. Two methods are employed for demonstrating autolysis; (1) the anti-septic method, (2) the aseptic method. The method of Salkowski which is commonly employed depends upon the employment of antiseptics. The organs are ground in a grinder and placed in a sterile vessel with some antiseptic such as toluene or chloroform. The tissue is allowed to stand for several days or weeks and subsequently examined. It is found that the coagulable nitrogen is considerably reduced, while the non-coagulable nitrogen in the form of albumose, peptone, ammonia, amino-acids, etc., is increased. The aseptic method removes organs and tissues under aseptic conditions and preserves them under the same conditions. Danger of infection is very great and the work of Wolbach, Saiki and Jackson shows that in the case of the dog it is practically impossible to secure aseptic organs, because of the fact that bacteria are usually present in such organs before they are removed from the body. The change appears to be due to an enzyme or enzymes liberated upon the death of the cell and operating best in a slightly acid medium (see Bradley). Acid operates probably by alteration of the protein substrate upon which enzymes act. Nevertheless, a degree of acidity may be reached which is sufficient to inhibit the ferment action. Oka has confirmed the general principle that the more highly differentiated parenchymatous cells undergo autolysis more readily than the cells of the supporting tissues and the cellular derivatives of the latter. Glandular cells meeting death during active digestion undergo autolysis more readily than when at rest. Certain types of cell granules autolyze more rapidly than do those granules which have a special affinity for carmine.

Morphological Changes in Death.—Changes noticed in the exterior of the body following death have been indicated in the section given above. In a general way the same is true of the changes seen in the internal viscera following death. The most important changes in the viscera depend upon the processes of autolysis and putrefaction. If organs and tissues be examined immediately after death no change is noticed other than dependent hyperemia. If, however, degenerative changes have had time to occur, the organs show softening. Sometimes swelling may appear, the result of imbibition of water probably due to changes of the tissue colloids by which they become hydrophilic. This swelling and softening of organs very closely resembles and is easily confused with cloudy swelling. The softening may go on to actual liquefaction, a change particularly noticeable in the medulla of the adrenals and also seen commonly in the spleen. Materna has recently presented evidence that the

central softening of the adrenal is not essentially a postmortem change but occurs before death, particularly in cases of infectious disease; the process is due in these cases to occlusion of blood vessels, hemorrhage and other changes. Microscopic changes may occur very early after cell death, particularly in the reaction of cell granules to certain dyes. Subsequently, the normal granularity and even the outline of the cell may be lost, the cytoplasm may show a hyaline appearance and later coarse granules. Certain substances not ordinarily visible under the microscope may become so after autolytic and putrefactive changes, such as fats, myelin and other lipoids. Neutral red and methylene blue do not stain the nuclei of living cells, but practically as soon as death has occurred the nuclei take these stains. This change appears before there are morphological alterations of the nucleus. Later, however, the nucleus is likely to show paler staining and may finally undergo complete lysis. If a sufficient time elapse after death, mitotic figures which were in evidence at the time of death may go on to complete division and show the resting stage of the nucleus. Thus, the number of mitotic figures seen in a given preparation may not actually indicate the number present at the time of death. All these changes which have been described serve to emphasize the importance of examination of organs and tissues as soon after death as possible. Immediate fixation of tissues serves to preserve appearances more nearly like those in the living organism than is true if fixation be delayed.

Necrosis.—Necrosis indicates death of a group of cells, a part of tissue or an organ, in continuity with the living body. The most familiar example is death of an extremity or part of an extremity due to occlusion of an artery, usually spoken of as gangrene. Similarly, a part or even an entire viscus may die as the result of the occlusion of the main artery or of its smaller branches. Burns of the third degree produce necrosis of the tissue. Such burns differ from the ordinary reddening or blistering in that there is destruction of the underlying skin and even of deeper structures.

Etiology.—Necrosis may be produced mechanically in a variety of ways. Of the utmost importance in this connection is trauma. Prolonged pressure on the tissues, or cutting by means of a sharp instrument cause necrosis, the former operating so as to produce large areas of necrosis and the latter producing necrosis in the track of the instrument. A characteristic form in which necrosis may appear as a result of prolonged pressure is known as decubitus. This signifies a chronic ulceration, which appears on the buttocks, over the sacrum, heels or other bony prominences. The ulcers arise usually after long confinement to bed and occur especially in debilitated patients and also in those suffering from certain lesions of the nervous system, where trophic disturbances are supposed to occur. Hence, factors other than pressure are operative, and the most important of these are probably a general lowering of vitality and decreased nutrition. Injury to the cytoplasm of a cell does not necessarily lead to death but injury to the nucleus is probably never survived. This is apparently due to the importance of the part played by the nucleus in metabolic activity. The thermal causes of necrosis include both heat and cold. The activity of these

depends upon the degree of temperature and the duration of exposure. Temperatures of 45°C . applied locally may produce necrosis provided exposure is prolonged for five or ten minutes. Similarly, a temperature of 53°C . may produce necrosis following an exposure of three minutes. Local temperatures in the neighborhood of 100°C . may produce necrosis so slight as to be not easily demonstrable, but indicated by the subsequent appearance of inflammation. Prolonged exposure to temperatures of about 100°C . produces deep necrosis of the tissues. Momentary exposure to higher temperatures may produce the same result. Less high degrees of temperature, when affecting the entire body, may lead to more serious changes, and it is stated that mammals succumb at temperatures of 47°C . The essential change appears to be the coagulation of cell proteins, and Halliburton has found that in practically all tissues there are globulins which coagulate at temperatures of 45° to 50°C . Such coagulation may upset the colloidal equilibrium of the cells so as to lead to death. Most enzymes resist temperatures of 60° to 70°C . and are therefore probably of

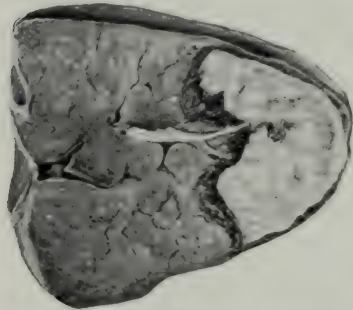


FIG. 30.—White or anemic infarct of spleen, in the gross.

little significance in necrosis due to higher temperatures. Cold is not likely to produce necrosis unless there is actual freezing of parts. When freezing occurs the circulation is necessarily interrupted, partly by constriction of small vessels, partly by increased viscosity of the blood, and partly by the occlusion of vessels by hyaline thrombi. It is probable that interruption of circulation is of the utmost importance in this type of necrosis. This general statement is supported by the resistance to cold of unicellular organisms and of certain isolated

cells of metazoa such as blood cells, ciliated and surface epithelium. Cells rich in water may be injured by the formation of ice crystals, so that upon subsequent thawing they do not survive. Other physical causes of necrosis include electricity, light, the x-ray, and the rays of radium. The electric spark produces areas of necrosis in the course of the spark. The passage of the electric current, if of sufficient amperage, may lead to cell death or death of the entire organism. Wells suggests that "the electric current causes a migration of ions toward one or the other pole of the cell, in this way separating the movable inorganic ions of the ion-protein compounds of the cell, from the immobile colloidal proteins with consequent serious alterations in the chemistry of the cell." This may serve to explain the vacuolization of cells dead as the result of the electric current. In man, death from the electric current is preceded by fibrillation of the heart and is accompanied by liberation of gases about blood vessels, hemorrhages and nerve cell degenerations. Light rays may produce death of unicellular organisms, as the result of the action of the short wave length rays. The longer wave lengths require oxygen and probably depend in part for their activity upon oxidation, but this does not appear to be true of the ultraviolet rays. In man, strong sunlight may produce slight necrosis and

inflammation; in the presence of sensitizers such as the porphyrins it may produce more severe necrosis and somatic death. Prolonged light exposure may injure ferments and other similar bodies, but in the presence of sensitizers such as eosin, rose bengal, numerous metals and their salts, the activity of light may be much augmented. Sensitization may also intensify the destructive action of light upon organic substances and living cells. The x-ray produces necrosis provided the dose is sufficiently great. The effect appears to be directly upon the cells involved and causes deteriorative changes in the nuclei before the cytoplasm becomes affected. No cells are immune, but the effect is seen particularly in the lymphoid apparatus where necrosis of germinal centers is pronounced. Hall and Whipple have demonstrated that suitable doses given over the abdomen produce necrosis of the intestinal epithelium. Surface burns by x-rays show extensive necrosis which heals slowly. Radium rays have essentially the same effects.

The chemical causes of necrosis include particularly the corrosives such as strong acids, strong alkalis and phenol. The skin of different individuals shows variable degrees of susceptibility to necrosis by phenol, but this does not appear to be true of the corrosion produced in internal viscera such as the stomach. The direct effect of concentrated corrosives is coagulation of, and in some instances chemical combination with, the cell proteins. Dilute phenol may cause necrosis by producing conglutination of red corpuscles with consequent obstruction of small vessels. Any chemical which coagulates the protoplasm or destroys the enzymes of a cell leads to its death.

Toxic causes of necrosis include certain chemical poisons and the poisons of parasitic or saprophytic organisms. In the former group are included such substances as bichloride of mercury, cantharidin, uranyl nitrate and other substances which, circulating in the blood appear to have a particular affinity for cells of the kidney, although other parenchymatous cells are affected to a less degree. In the later stages of poisoning by bichloride of mercury the mucosa of the lower ileum may become necrotic, probably because of excretion of the poison in this situation. The poison produced in the condition known as eclampsia and in acute yellow atrophy of the liver produces necrosis of liver cells. This is also true of phosphorus, chloroform, hydrazin, and other agents. Any marked alteration in the hydrogen ion concentration, either toward acid or alkaline reaction, may lead to the death of the cell.

Bacteria produce poisonous substances which lead to necrosis of the surrounding cells. This is particularly true of pyogenic bacteria. These are likely to lodge in small blood vessels, in interstices of the skin, in tonsillar crypts, or other situations, where they proliferate and form masses of organisms which become surrounded by an area of necrotic tissue. Local necrosis may be produced on injection of diphtheria toxin and certain other toxins. The general effect of these toxins, however, even when leading to somatic death, does not necessarily lead to necrosis. As Auer has shown it is possible so to concentrate the reacting substances in anaphylaxis as to produce necrosis.

Of particular importance is necrosis due to occlusion of the blood vessels. The occlusion of a supplying artery to a part, provided anastomosis is not sufficient to maintain nutrition, leads to a series of changes, ultimately including necrosis, called infarction. The infarct is likely to be irregularly conical in shape corresponding to the area of distribution of the artery and its branches. Such occlusion of arteries may be due to lodging of small foreign particles in the blood stream, spoken of as emboli; it may be due to occlusion of vessels by intravascular clotting or thrombosis; it may be due to occlusion by arteriosclerosis of different forms; it may be due to prolonged constriction of the vessels, probably of nervous origin; or may result from compression of the

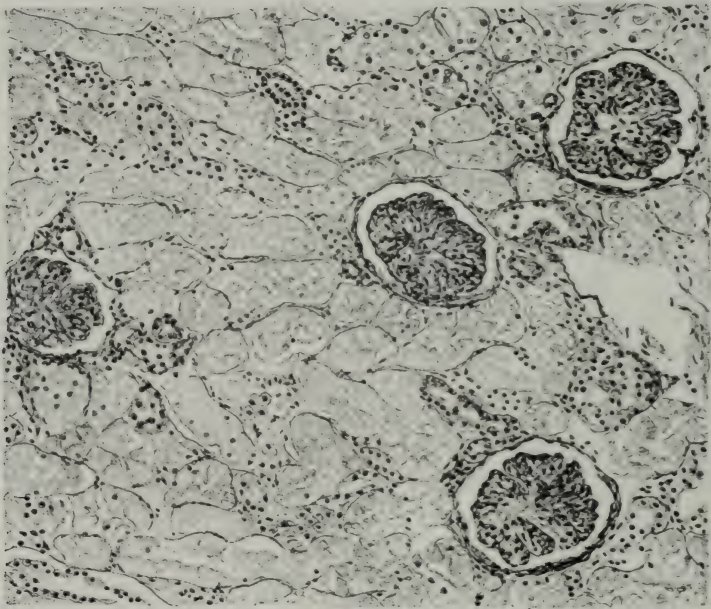


FIG. 31—Necrosis of renal epithelium in accidental male fern poisoning. The cells of the convoluted tubules show marked cytoplasmic swelling, loss of cellular outline and partial or complete lysis of nuclei.

vessels, as for example, by tumor growth. The necrosis of infarction is due to removal of blood supply. Certain types of cells, however, appear to resist this lack of nutrition for longer periods than others. Ganglion cells are especially susceptible. In a general way parenchymatous cells are much more susceptible than connective tissue cells and the surface epithelium of the skin. The cause of necrosis in infarction is probably a combination of factors, including lack of oxygen and deficient nutrition. Catabolic and anabolic changes are no longer balanced, organic acids probably accumulate and the proteolytic enzymes continue to operate even after the death of the cells, especially in the acid medium produced. Necrosis is also said to be due to alteration of the nerve supply, so that the ordinary nutritional and metabolic processes in the tissues are cut off. Such a process of necrosis is seen in atrophic necrosis or ulcer of the cornea. In association with the loss of tissue which is seen in these ulcers, there

is an anesthesia of the cornea, and it seems likely that the ulcer is due to unsensed traumatism resulting from this anesthesia, rather than directly to the nerve lesion. There is no doubt that muscle atrophy of certain parts may be the result of lesion of the motor ganglia supplying that part, but that this is due to trophic disturbance rather than simple lack of use is a matter of great doubt. In anesthetic leprosy there is often necrosis of fingers and toes but here again the difficulty is probably due to trauma and infection, rather than to interference with nerve regulation. Similarly, in those curious ulcers which develop on the feet, the so-called perforating ulcers of the feet or "mal perforant du pied," there is an associated anesthesia. Raynaud's disease shows symmetrical necrosis of peripheral parts, particularly the toes and fingers, and is associated with functional nerve lesions. The disease is not trophic in the ordinary sense, but depends almost certainly upon prolonged constriction of arteries due to nerve stimulation. Certain diseases of the nervous system associated with anesthesia, such as syringomyelia, may lead to necrosis because of loss of sensation.

Morphology of Necrosis.—The gross morbid anatomy of necrosis can best be described in the various forms which are to be discussed, because these forms are likely to show important differences in the naked eye appearance. Microscopically, however, the changes are fairly uniform. Three important alterations are found in the nucleus, namely, karyolysis, karyorrhexis, and pyknosis. The term karyolysis signifies solution of the nucleus. There may be, however, intermediate stages in the lysis of the nuclei in which the nucleus stains less deeply than normally. Nevertheless, it must be assumed that the nucleus is dead with the beginning of solution. Karyorrhexis signifies fragmentation of the nucleus whereby the nuclear substance is broken up in small particles. These take the nuclear stain deeply and sometimes are difficult to distinguish from bacteria, but the fragments are of irregular size and by reasonably careful study can easily be identified. Pyknosis indicates reduction in size and condensation of nuclear material, to form a solid, deeply basic stained body. In addition to these more important changes, the nucleus may sometimes show vacuolization in the process of necrosis. This change, however, may be associated with other lesions and is not diagnostic of actual death of the cells. These alterations of the nucleus are not necessarily sequential and may be quite independent of each other, but karyolysis is the final stage and may affect the nuclei, either primarily or as the sequence of karyorrhexis, pyknosis or vacuolization. The cytoplasm of the cells shows primarily those changes which have been described in cloudy swelling. Subsequently, however, cells may show either very coarse granules in the cytoplasm or hyaline transformation. Ultimately, cell

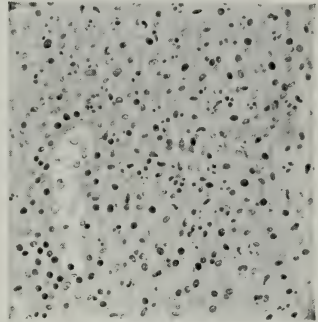


FIG. 32—Necrosis of lymph node in typhoid fever. Many nuclei take the stain poorly and are the seat of early karyolysis, others are small and deeply stained, exhibiting pyknosis. Deeply stained nuclear fragments are common.

outline is completely lost and the altered cytoplasm of neighboring cells fuses. As autolysis proceeds the material disappears, very largely by absorption of the fluid products of autolysis. Fragments of cells and of nuclei may be taken up by phagocytic cells, transported to neighboring situations and ultimately destroyed. The presence of dead tissue in the body is irritant to the surrounding living structures, and gives rise to the sequence of changes described as inflammation. This results in the infiltration of migrating blood and tissue cells and finally to growth of new blood vessels and connective tissue. The new blood vessels and connective tissue collectively are called granulation tissue, and undergo a series of alterations with the final production of a scar. Uninfected dead tissues give rise to only slight acute reaction and the process is seen almost solely as fibrosis.

Coagulation Necrosis.—This form of necrosis is best exemplified by the so-called anemic or white infarct which is an area of local death of tissue, consequent upon the obstruction of its supplying blood vessel. In the early stages, the area is likely to be swollen, somewhat granular, pallid or clay colored, soft, relatively dry and friable. It is usually sharply defined, projects in the cut surface and is likely to be surrounded by a small zone of redness due to early reactive inflammation. Microscopically, the changes indicated above are to be found. Such necrosis is given the name coagulation because of the fact that not infrequently fibrin, or so-called fibrinoid, formation may be demonstrated. As a rule, however, the fibrin is so small in amount as to be shown only by special staining. The necrotic material itself is not soluble in water, solutions of neutral salts or dilute acids and alkali, but a salt solution extract of such areas may readily coagulate. If bacterial infection go hand in hand with necrosis, fibrin may be present in larger amounts. Fibrinoid is a substance which forms a network similar to that of fibrin, but does not react to stains in exactly the same fashion. Instead of taking the acid stain it is more likely to take the basic stain. As time goes on and the fluid is removed, the area of necrosis loses its swollen appearance and shows decrease in size, increased firmness, and retraction. If it be not too large it ultimately becomes entirely substituted by scar tissue, but if its size be too great for this process it becomes surrounded by an area of fibrous tissue and is said to be encapsulated. Gierke includes in this group of necrosis, focal necrosis due to infectious disease and Zenker's degeneration or necrosis of voluntary muscle. Zenker's hyalin has been described in connection with degenerations but it must be admitted freely that this change is a necrosis rather than a simple degeneration.

Cheesy or Caseous Necrosis.—This form of necrosis is particularly well exemplified in the necrosis of the center of a tubercle. The gross appearance gives the condition its name. It is usually found in fairly well circumscribed areas and is characterized by its resemblance to cheese. This differs from other forms of necrosis, in that the degenerative and necrotic changes of the cells lead to the formation of fat and lipid products which may readily be demonstrated by special staining. The percentages of fat, cholesterol and other lipoids vary considerably in different specimens and in the hands of different

investigators. Caseous necrosis is so complete that no remnant or outline of the original tissue remains. The direct cause of caseation is unknown. Whether it is due to the wax of the tubercle bacilli, some soluble product of the bacilli, enzymes from the surrounding lymphocytes or other agent has not been finally determined. Microscopically, the cellular changes are similar to those described above except for the fatty change. This means that with ordinary stains, the condition in itself is not characteristic. With the diagnosis, however, of tuberculosis of the area, it is very easy to assume that the necrotic change is caseous in character. Cheesy necrosis may be seen in conditions other than tuberculosis, particularly in cysts with necrosis of the contents, but for all practical purposes the change is confined to tuberculosis. The necrosis in the gumma of syphilis is much the same histologically but grossly more closely resembles a gummy or putty-like substance than cheese. In certain instances of caseous necrosis, fibrin can be demonstrated, and for this reason Gierke includes caseous necrosis as one of the varieties of coagulation necrosis.

Colliquation or Liquefaction Necrosis.—This indicates an alteration of the dead tissue so as to produce fluid. In other words, the area softens considerably and finally liquefies. The change may follow any of the other forms of necrosis and is generally considered to be the result of activity of ferments or autolytic agents. Thus the infarct of kidney and spleen may finally show colliquation necrosis and the same is true of cheesy necrosis. This is particularly well exemplified in the softening of tuberculous areas of the lung so that the material is expectorated as a fluid or semifluid mass. The same general process operates in the softening of pneumonic exudate so that the material can either be absorbed or expectorated, and in the softening of abscesses so that the contents can be discharged. Infarcts of the central nervous system are not likely to show the early stage of coagulation necrosis but rapidly go on to liquefaction, producing cystic areas filled with fluid which at first are surrounded by living nerve substance, and ultimately become encapsulated. The most common example of colliquation necrosis is seen in the liquefaction of pus in abscesses or other areas of suppuration.

Fat Necrosis.—The particular type of death of fat included under this heading is that seen most commonly in man as a result of acute destructive disease of the pancreas. The fat of the neighboring omentum, of the pancreas itself, sometimes of the abdominal walls and even that of more remote situations such as the liver, shows the appearance of small, pale yellow or white nodules closely resembling soap. As a rule, somatic death results from the causative disease, so that subsequent changes are not observed. In experimental work, however, it is known that the lesion leads to reactive inflammation in the neighborhood, which finally results in the complete disappearance of the fat and healing of the area. The death of the fat is due to liberation of pancreatic ferments resulting from the destruction of part of that organ. Wells has made extensive experimental studies of this condition, and finds that the injection of fresh pancreatic extract and even of commercial

pancreatin can produce these lesions. Neither pure lipase nor pure trypsin is capable of producing the condition, nor can mixtures of these ferments from organs other than the pancreas. Whether or not the lipase of the pancreas is different from that of the blood or of other organs and tissues, has not been definitely determined, but it seems likely that the combination, as provided by the pancreas, of both lipase and trypsin has an especial action in producing fat necrosis. It is possible that the trypsin first operates upon the cellular tissue causing death and that subsequently the lipase splits the fat. It is certainly known that fat splitting occurs with the consequent production of fatty acids and glycerol. The glycerol is absorbed and the fatty acid remains in situ, where part of it combines with alkali to form soaps and the other part may crys-

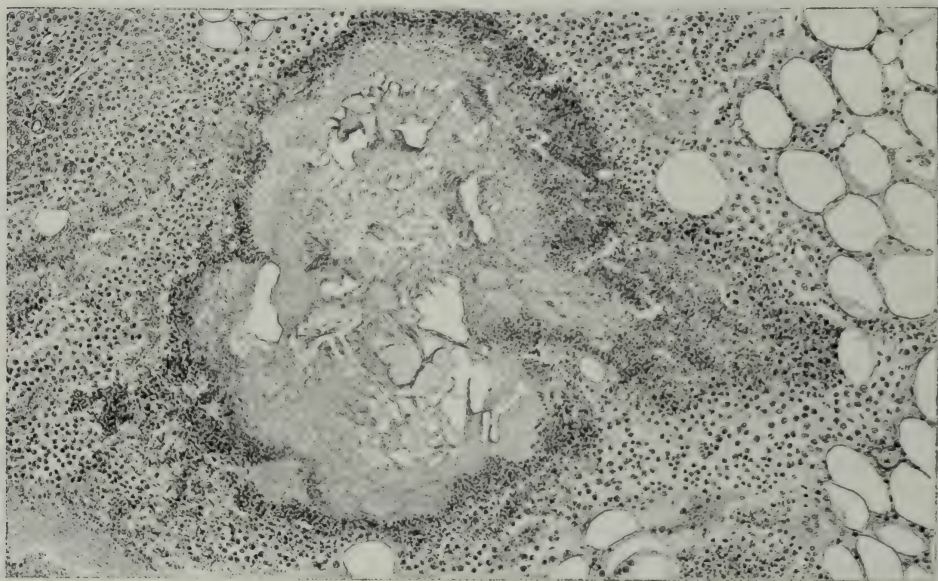


FIG. 33—Experimental fat necrosis, showing disappearance of fat cells, granular mass of detritus acicular spaces of fatty acid crystals and reactionary infiltration of polymorphonuclear leucocytes.

tallize. The activation of trypsinogen probably depends upon a kinase furnished by the leucocytes or other cells. In man, as has been stated, the most common cause of the lesion is acute pancreatitis, but destructive lesions of fat such as those produced by traumatism may similarly result in fat necrosis (see Parsons). Histologically, there are found necrosis of the parenchyma of the fat cells with the various changes of necrosis in their nuclei. Often there are fairly large foci of complete destruction of tissue. The fat has disappeared or, when soap has been formed, the latter is likely to take the basic stain, probably because of the presence of calcium, and appear as a finely granular substance in the oil spaces. Crystallization of the fatty acids and removal of these crystals by the ordinary process of embedding, results in the formation of acicular spaces in the prepared tissues. Fresh tissue stained by Benda's method (copper acetate) gives the typical green color of fatty acid. The surrounding living

tissue may show reactive inflammation with extensive infiltration of polymorphonuclear leucocytes, lymphocytes, and endothelial cells. The destruction of blood vessels in the course of the process may lead to hemorrhage, visible sometimes grossly but often only microscopically. The glycerol liberated, the amount of fatty acids formed, the amount of soap formed, even though it might be slightly soluble, is not sufficient to account for the intoxication which may

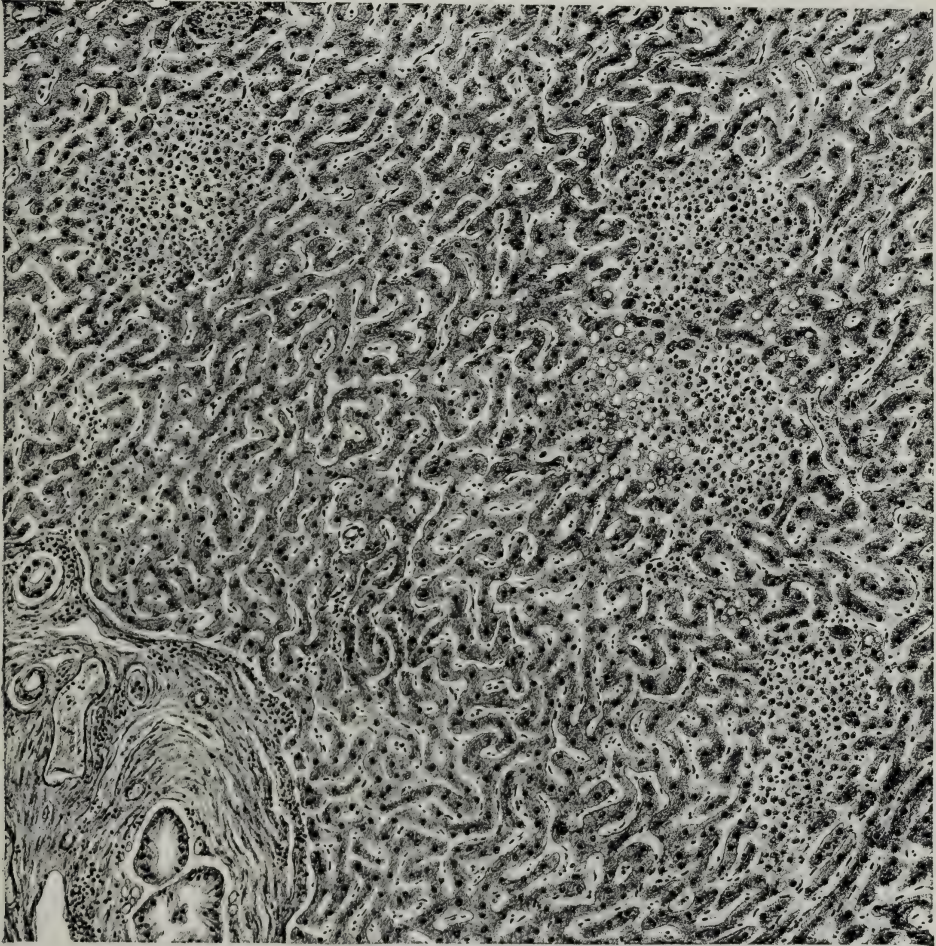


FIG. 34.—Focal necrosis of liver in typhoid fever.

accompany this condition, and it is assumed that the causative disease rather than the fat necrosis leads to the severe symptoms.

Liver Necroses.—These represent an important chapter in both special and general pathology. *Focal necrosis* of the liver is seen in connection with infectious diseases, most notably typhoid fever, although in diphtheria, scarlatina, measles, and other acute infections, necrosis, anatomically identical with that of typhoid fever, may occur. The areas of necrosis are so small that they are rarely, if ever, visible to the naked eye. Microscopically, they occupy a small

part of the lobule of the liver; they appear as rounded areas of complete necrosis of the liver cells accompanied by infiltration of other cells, particularly large mononuclears mixed with a certain number of lymphocytes and occasionally with polymorphonuclear leucocytes. Except for this infiltration there is likely to be no other reaction. According to Mallory, these areas of necrosis are due to blocking of the liver sinusoids by large endothelial cells from the spleen and other portions of the abdominal lymphatic apparatus. In typhoid fever these cells multiply in the lymphoid apparatus, and may become free so as to enter into the blood circulation and thus gain access to the liver. Karsner and Aub in a study of experimental necrosis of the liver due to injec-

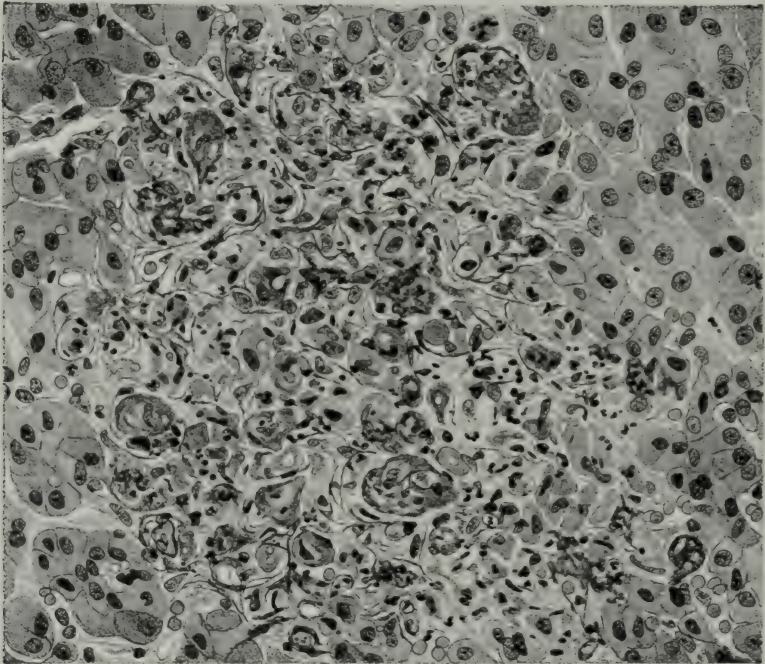


FIG. 35—Focal necrosis of liver in scarlet fever, showing necrotic and partial disappearance of cells, with infiltration of endotheliocytes and polymorphonuclear leucocytes.

tion of specific hemolytic immune serum, come to the conclusion that obstruction of the capillaries alone is of minor significance and that more important probably is some cytolytic element conveyed by the cells. Jaffè, however, maintains that the proliferation of the Kupffer cells of the liver in focal areas leads to the lesion, and that if necrosis be actually present it is secondary to the focal proliferation of these cells. *Central necrosis* of the liver is to a certain extent dependent upon passive hyperemia. It affects the cells near the central veins and there is, in the acute cases, no indication of fixed tissue reaction. It has usually been assumed that damming back of blood into the central vein and neighboring capillaries, as the result of prolonged passive hyperemia, leads to such deterioration in the nutrition of the parenchymatous cells in that neighborhood that they finally undergo necrosis. Mallory, however,

in a careful study of this condition comes to the conclusion that passive hyperemia alone will not produce central necrosis but that, in addition to the passive hyperemia, there must be present a circulating poison of some sort which so reduces the resistance of the cells that they cannot survive the nutritional reduction incident to passive hyperemia. The central cells show all the changes of necrosis, associated, as a rule, with some dilatation of the central ends of the liver sinusoids. The change is so minute as not to be observed by the naked eye.

Various poisons apparently have a particular affinity for liver cells. *Chloroform* is likely to produce well marked necrosis affecting first the central zone of the lobule and subsequently the middle and even the peripheral zones. It can easily be produced experimentally by having animals inhale chloroform for about one hour. Progressive studies show rapid healing and complete reproduction of the liver cells. Phosphorus also produces necrosis of the liver affecting primarily the peripheral or middle zone and associated with extensive fatty changes. Hydrazine hydrochloride produces extensive necrosis throughout the entire lobule from which the liver may readily recover. Certain poisons generated in eclampsia and in acute yellow atrophy of the liver produce extensive necrosis. In eclampsia, necrosis is likely to be irregularly distributed in the periphery of the lobules. In acute yellow atrophy necrosis is likely to be primarily either central or mid-zonal, and is associated with extensive fatty changes. Little is known of the sequence of changes in eclampsia, but in acute yellow atrophy the parenchyma destroyed in the course of the disease is not likely to be reproduced, and the effort at regeneration of such a condition is found to be almost entirely confined to the bile ducts. The latter changes will be considered more extensively in discussing diseases of the liver.

Gangrene.—Gangrene signifies necrosis to which is superadded invasion and multiplication of saprophytic organisms. The condition may affect any part of the body as the result of invasion of organisms through wounds or interruption of continuity of skin surface, or through the respiratory, intestinal, or genito-urinary tract. Affecting extremities or other parts in connection with the skin surface, a clinical distinction between so-called dry and wet gangrene has attained widespread use. While this distinction may serve a useful purpose it must be emphasized that dry gangrene is simply bland infarction of a peripheral part and that wet gangrene is true gangrene as defined above. Dry gangrene, or bland infarction, as it should be called, results from occlusion of an artery which completely cuts off the circulation of blood and fluids so that the drying effect of air can be manifested. Because of deteriorative changes in the blood and blood pigments which remain in the part, discoloration appears. This is usually green, or yellow and finally dark brown or black. Drying of skin and other parts leads to a parchment-like skin with reduction in the size of the part, wrinkling of the skin and the general appearance spoken of as mummification. The presence of the dead tissue leads to inflammatory reaction in the neighboring living tissue so as to form the so-called line of demarkation. This may be emphasized by liquefaction of that necrotic tissue situated near enough to the

living tissue to imbibe fluids and their ferments. Wet gangrene, which is a true gangrene according to our definition, may appear in extremities or internal viscera. The invasion of saprophytic bacteria gives rise to rapid degenerative changes in the dead tissue, leading to liquefaction, gas formation and the

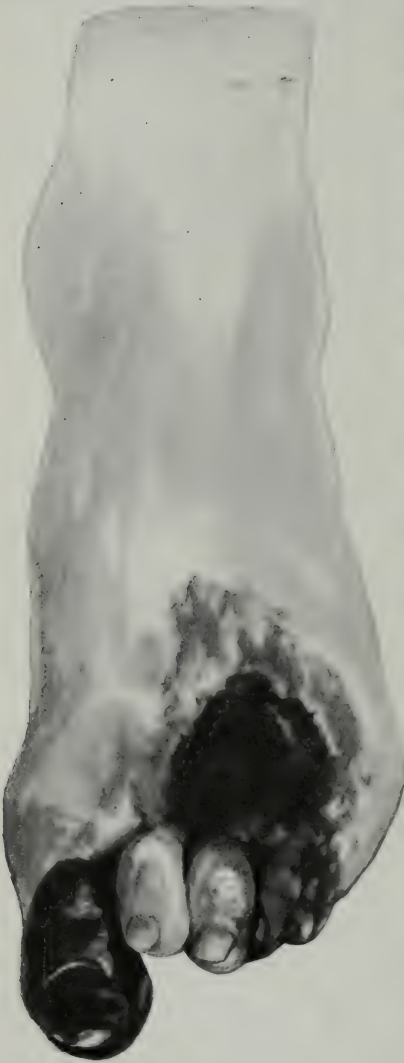


FIG. 36—Gangrene of foot.

development of foul odors. Discoloration appears but is very much modified by the moisture and gas formation. Owing to the irritant products of the bacteria, the surrounding tissues may react with considerably more violence than is seen in "dry gangrene." The absorption of the toxic products of these saprophytic bacteria leads to the general symptoms of sapremia and sometimes results fatally. Histologically, the tissues of dry gangrene (bland infarction) show the usual changes of necrosis, somewhat modified by desiccation. Many of the nuclei do not undergo complete solution, but pyknosis and karyorrhexis are likely to be common. The cell outline may not be lost. The failure of active progress of the usual histological changes of necrosis is probably due to desiccation of the tissues, which inhibits the activity of autolytic ferments. In moist gangrene the solution of the tissues is likely to be so complete that no remnant of cells or nuclear structure is to be found.

Gas Gangrene.—The importance of gas gangrene was emphasized by the experiences of the Great War. Access of micro-organisms is provided by crushing wounds which destroy a considerable amount of tissue, permit introduction of the organisms into deep areas where there is little or no access of air, and thus provide favorable nutritional conditions for the saprophytic, anaërobic bacteria. The organism of most

importance and of most common occurrence is the *bacillus aërogenes capsulatus* of Welch or, as it is sometimes called, *bacillus perfringens*. Commonly associated are *vibrio septique*, the *bacillus oedematiens* and a facultative streptococcus. Bull and Pritchett have demonstrated that the toxin of the *bacillus aërogenes capsulatus* can, upon injection, produce necrosis of the tissue. This being true, it seems likely that the disease extends because of neighboring necrosis due to absorption of the toxin, thus providing

suitable condition for further growth of the saprophytes. Weinberg and Seguin point out that the vibrión septique produces similar disease, but that the bacillus œdematiens probably serves simply to accentuate the action of other bacteria. Grossly, the part affected is swollen, discolored, has a foul odor and upon palpation is found to crepitate. Gas formation may be so extensive as to produce not only crepitation but visible bubbles and surface blisters. The discoloration which is due to secondary changes in blood and blood pigments is similar to that of the ordinary forms of gangrene. Muscle the seat of this condition shows first failure to contract on stimulation, followed by a peculiar, pale, glossy appearance resembling that of the muscle of fish. This is followed by extensive softening associated with gas formation and dark greenish-brown or black discoloration. Microscopically, the changes seen are similar to those seen in other forms of necrosis, except that even with ordinary stains the bacilli may readily be demonstrated. This condition was found in soldiers because of contamination of wounds by infected earth, particularly those wounds associated with extensive destruction of tissue. The same is true of cases in civil life where certain wounds are similarly contaminated. This is not infrequently found in injuries to coal miners or other workers who come in contact with earth infected by animal carriers of the organisms.

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CHAPTER V

MINERAL INFILTRATES AND CONCREMENTS

CALCIFICATION.

INTRODUCTION.

PATHOLOGICAL INFILTRATION OF CALCIUM.

LOCAL CALCIFICATION.

METASTATIC CALCIFICATION.

PATHOLOGICAL OSSIFICATION.

HETEROPLASTIC OSSIFICATION.

CHEMISTRY OF CALCIFICATION.

CRYSTALLINE DEPOSITS IN TISSUES.

URATES.

CHOLESTEROL.

CONCREMENTS.

BILIARY CONCREMENTS.

CHEMICAL COMPOSITION.

MECHANISM OF FORMATION.

URINARY CONCREMENTS.

CHEMICAL COMPOSITION.

MISCELLANEOUS CONCREMENTS.

PANCREATIC AND SALIVARY.

INTESTINAL, ETC.

PHLEBOLITHS.

CORPORA AMYLACEA.

PSAMMOMA BODIES.

Introduction.—The metabolism of calcium plays an important part in the body economy. This element is ingested with solid food and liquids and is excreted in the feces and to a slight extent in the urine. The exact form in which it is retained in solution in the blood is not definitely known, but it seems probable that its solvency depends in part upon the colloidal proteins and in part upon the carbon dioxide concentration of the blood. The normal concentration of this element in the blood is approximately 1 : 10,000 which is almost the point of saturation for the forms of salt in which it occurs. Indeed Holt, LaMer and Chown find that tertiary calcium phosphate is present in supersaturation. Throughout life calcium participates in bone formation; by its deposition in cartilage and osteoid tissue during the growing period, and in osteoid tissue alone after endochondral growth of bone has ceased. No less important is the part that calcium plays in connection with the irritability of muscle and nerve.

In diseases such as rickets, osteomalacia and some forms of tetany, alterations in the metabolism of calcium lead to local as well as general pathological manifestations. These will be considered under the heading of diseases of bones and diseases of the ductless glands.

Pathological Infiltration of Calcium.—Although bone is the only situation in which calcium is deposited normally, yet it may be found in many pathological conditions. Most frequently, it is deposited in poorly nourished or dead tissues. Thus, it is found in areas of necrosis and in interstitial substances. It is also frequently deposited in the form of calculi. A third form of deposition is called calcium metastasis or metastatic calcification. This metastasis signifies

deposition in living tissues such as stomach, kidney and lung, apparently as the result of transfer of the calcium from diseased bone (osteomalacia, destructive tumors).

Local Calcification.—The local deposition of calcium is seen most commonly in the connective tissue of larger arteries as a part of the process of arteriosclerosis. In the course of arteriosclerosis, connective tissue is formed in excess, following which it becomes hyaline and then necrotic. As a sequence of the necrotic stage, or sometimes earlier, calcium is deposited. It may be found in the intima or in the media. Calcification is not uncommon in areas of chronic inflammation where essentially the same process takes place, namely fibrosis,

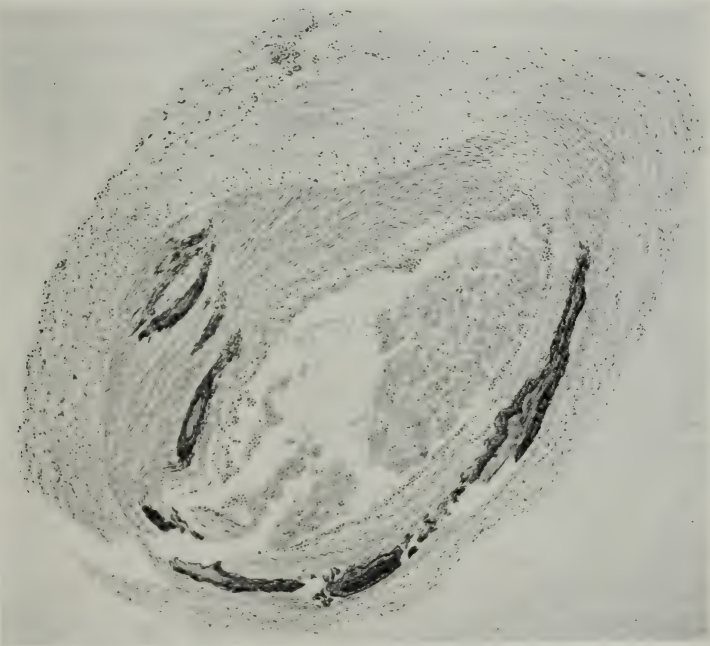


FIG. 37—Calcification in media of small artery in senile arteriosclerosis.

hyalinization, necrosis and calcification. Calcification so frequently occurs in areas of old chronic inflammation, that no particular reaction to the presence of this foreign substance is seen, but when it is deposited in active living tissues, a surrounding area of reactive fibrosis, sometimes with foreign body giant cells, may be found. This may be seen in pleura, pericardium, peritoneum and other serous membranes. Occasionally, infarcts or other necrotic areas become the seat of calcification. The caseous necrosis in foci of tuberculosis is particularly prone to calcification. Necrotic material in old cysts and inspissated collections of pus not infrequently calcify. Calcification of epithelium may be seen in mercuric chloride poisoning in the kidney. In fact, almost any type of cell may be the seat of calcification. Not only in dead tissue but also around foreign substances, calcium may be deposited. This is well seen in long standing trichinosis, in which the *trichinella spiralis* within muscle or within other tissues

may ultimately become calcified. Local areas of calcification may be of sufficient size to be observed grossly as dense, firm areas, usually pallid, giving a metallic sound when struck with an instrument, usually fracturing easily and producing crepitus after fracture. In the early stages of calcification, microscopic examination may show simply the presence of a number of fine granules. Not infrequently, however, the calcium may be found in the form of small globules measuring 20 micra or more in diameter, with a dense center and outer margin and sometimes distinctly laminated. These are referred to as calcospherites. As the process advances, the granules or calcospherites increase in number and fuse to form solid granular masses, in which the identity of the calcospherites is usually lost. Calcium takes the basic stain, and small masses with their neighboring granules sometimes resemble bacteria, but the lack of uniformity in size and outline of the calcium granules serves for ready differentiation. As a rule, the appearance is quite characteristic but sometimes special stains are necessary. The Von Kossa method is satisfactory for the demonstration of calcium in fresh or fixed tissue.

Metastatic Calcification.—In the discussion given above, emphasis has been placed on the belief that in the usual type of pathological calcification some form of degeneration or necrosis precedes the calcium deposit, but certain observers express the view that this is not necessarily so, and that calcification may occur before the degenerative and fibrotic lesions. In the so-called metastatic calcification a degeneration in the ordinary sense does not precede the deposit of calcium metastases. Destructive lesions of bone, such as osteomalacia and tumors, may be associated with calcification in other situations, notably the lung, stomach and kidney. In the stomach the calcium is found in the tunica propria near the acid glands of the fundus. In the lung it is likely to be found near or in the walls of the tributaries of the pulmonary vein. In the kidney it is likely to be found particularly in the tips of the pyramids. Cases have been described in which calcification occurred in the large arteries, in the pulmonary veins and in the endocardium of the left side of the heart. Metastatic calcification is likely to show reaction on the part of the neighboring tissues, which leads to increased production of connective tissues and not infrequently to the formation of multinucleated foreign body giant cells. In recent years most of the metastatic calcification described has been in cases of multiple myeloma, with extensive bone destruction such as that reported by McConnell. Virchow regarded the calcification as due to transport from the diseased bones. Meyer and Cajori have demonstrated the decalcification of bone, with a proportionate reduction of phosphate, and in multiple myeloma the output of calcium is increased (Blatherwick). There is no definite information as to calcium level in the blood, but it is obvious that the amount furnished to the blood is high. In the situations mentioned, where acid is secreted, it has been assumed that the tissues immediately near the place of secretion are sufficiently alkaline to favor precipitation of calcium. This may also be true when carbon dioxide is regarded as an acid and account for lesions in lung and heart. On the other hand, it has

been suggested that in situations in the vascular system, the carbon dioxide is low in amount and precipitation is thus favored. It is doubtful that low carbon dioxide content would lead to precipitation unless it could be shown that the amount of calcium in the blood is above normal. That acid-base balance is of some significance is shown by the experiments of Rabl and of Butler, who found that extensive calcification can be produced in mice by feeding an acid diet

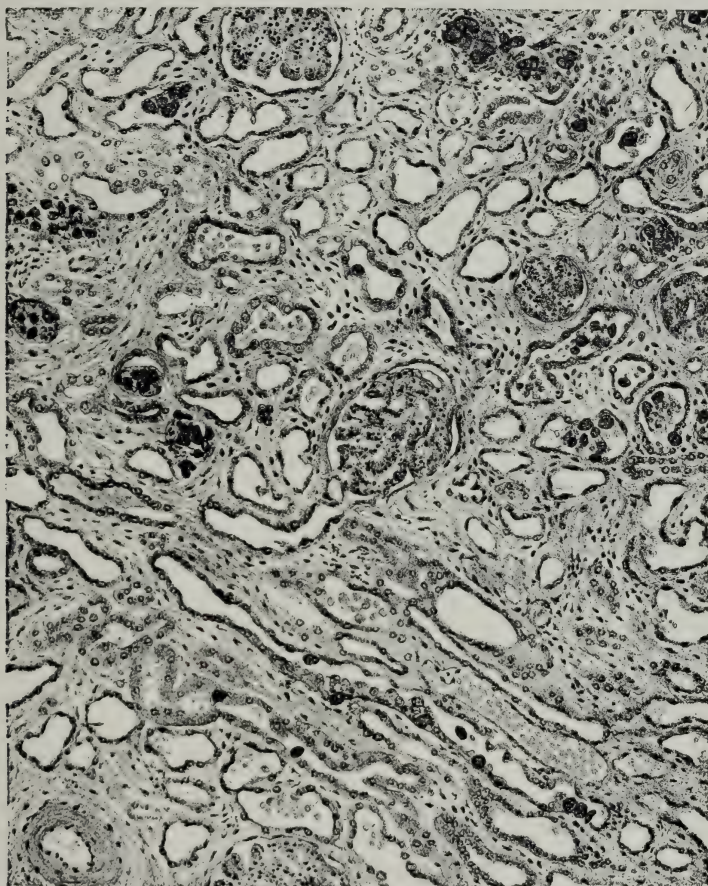


FIG. 38—Calcification in renal tubules in a case of mercuric chloride poisoning.

rich in calcium. Calcification is sometimes observed in chronic renal disease, and it seems more likely that an associated acidosis is of more significance than failure of calcium excretion, because most of the calcium is excreted through the intestinal tract. Similarly, calcification of tissues in old age may be quite as well attributed to alterations of acid-base equilibrium or to tissue degeneration as to liberation of calcium from senile atrophy of bone.

Pathological Ossification.—In normal ossification the calcium infiltrates cartilage, and by reason of cellular activity bone is formed. Bone has a very definite anatomical structure, including lamellæ, canaliculi and lacunæ, fea-

tures not present in simple calcification. With the exception of metastatic calcification, the deposit of calcium salts occurs principally in degenerate and dead cells, whereas in true bone formation there are living cells. Furthermore, ossification is accomplished only by the action of specialized connective tissue cells, whereas calcification occurs regardless of the type of cell involved in the preceding degeneration. The physical condition of hyaline connective tissue and of cartilage favors the deposition of calcium. In cartilage, this deposition precedes true bone formation due to the activity of osteoblastic cells. In advanced life, however, it is not infrequent to find extensive calcification of cartilage. This is in curious contrast to the fact that ossification in dead tissues is more likely to be encountered in old age.

Heteroplastic bone formation, the production of bone in areas where it is not normally found, has been reported in the kidney, pericardium, aorta, heart

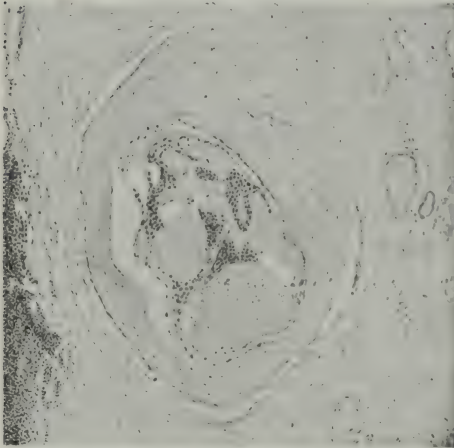


FIG. 39—Heteroplastic bone formation in an area of chronic inflammatory tissue. Note marrow formation and irregularity of lamellæ.

valves, veins, muscles, eye, and, according to Harvey, in nearly every organ of the body, not only of man but of many other animals. Although, in man, it is found usually in adults, it has been observed at eighteen months, three and eight years of age. It can be produced experimentally by ligation of the renal artery of the rabbit. After five or six weeks the kidney is found to be calcified and subsequently, particularly if collateral circulation be provided by anastomosis with omentum, ossification occurs. Harvey produced ossification in the aorta of rabbits by painting the adventitia with either 2 per cent. silver

nitrate or 2 per cent. cupric sulphate. He found primarily necrosis and calcification followed by ossification; occasionally an intermediate tissue was formed which bore a striking resemblance to cartilage. In man, however, cartilage has not been described in heteroplastic ossification. The heteroplastic bone is found in irregular masses, often associated with structureless areas of calcification. The lamellæ, lacunæ and canaliculi are arranged with variable degrees of irregularity. Bunting and others have noted the occasional presence of blood forming marrow, and Poscharisky maintains, probably incorrectly, that it is always present. The tissue surrounding the bone shows a chronic inflammatory change.

According to Wells, the mechanism of heteroplastic bone formation is not essentially different from that of endochondral ossification except that in the former, calcified material takes the place of primordial cartilage. The granulation (inflammatory) tissue erodes the calcareous area and the connective tissue cells undergo a functional metaplasia into osteoblasts. According to

Bunting the marrow cells in this process are derived from the connective tissue cells, but Maximow believes that they are derived from lymphocytes. There is little doubt that the presence of calcium stimulates these metaplastic cells to the function of osteogenesis. The physical presence of calcium salts or even of decalcified bone, implanted in the rabbit peritoneum by Liek failed to produce osteogenesis. The salts deposited are insoluble; it is not probable that the neighboring fluids are richer in calcium than the general body fluids, and it is therefore unlikely that there is a chemical influence favoring metaplasia. Ossification is favored by the presence of proper blood supply; complete elimination of blood supply delays ossification in the kidney of the rabbit; too rich a blood supply leads to neither calcification nor ossification. Wells states that "in order to have ossification of calcific deposits, certain conditions of relationship between calcium salts, fibrous tissues and blood supply evidently must be exactly met." The older hypothesis that the process is due to wandering osteoblasts, perhaps attracted to the calcareous area by chemotaxis, has been abandoned by most modern investigators, as is likewise the theory that the cells concerned in the process are lining cells of the invading blood vessels that have undergone metaplasia.

Bone formation in bony tissues may be stimulated in various ways. For example, the invasion of bone by malignant tumors, not osteogenetic in themselves may lead to ossification in the immediate neighborhood. The filling in of bony defects may be stimulated experimentally by implantation of dead but not of living bone, also by calcium salts. Extreme ossification is met with in the obscure Paget's disease of bones. Tumors of bone origin may produce bone, and if malignant, produce bone in the secondary nodules. Numerous other conditions are observed in which ossification proceeds to excess. Nevertheless ossification may be delayed or limited and there are disease processes in which decalcification occurs. These will be more fully discussed in the chapter on pathology of the bones.

Chemistry of Calcification.—In normal bones there is about 85 per cent. calcium phosphate, about 14 per cent. calcium carbonate and about 1 per cent. magnesium phosphate. With minor variations the same constitution is found in pathological bone formation and in calcification. Iron from areas of hemorrhage may be taken up by neighboring areas of calcification because calcium appears to have a special affinity for iron. In most areas of calcification there is a matrix of organic tissue. There are several important hypotheses concerning the deposition of calcium both normally and pathologically. It is essential in considering these theories to keep in mind the fact that degenerative changes practically always precede calcification, except in case of metastatic calcification. In numerous instances hyalin appears to be an especially favorable medium for calcification. In areas of necrosis that favor calcification, the circulation of blood is absent, and the only communication with the rest of the body is by the diffusion of fluids. Oxidation, therefore, is likely to be imperfect.

Changes may occur in the constitution of the necrotic area which favor the

precipitation of calcium from the fluids which pass through that area. As oxidation is reduced the amount of carbon dioxide found in these areas is small. Inasmuch as carbon dioxide plays a part in maintaining calcium in solution, this change might favor precipitation. Necrotic tissues, however, tend to become acid in reaction and it is possible that this may counterbalance the reduction in carbon dioxide. Of importance is the hypothesis of Lichtwitz. He calls attention to the precipitation of the colloids in necrotic areas as shown by granular changes in the cells. If the solution of calcium depend upon the colloid character of the menstruum, the reduction of surfaces of adsorption through this colloid precipitation would necessarily lead to precipitation of the calcium. There follows an attempt at reestablishing osmotic equilibrium by the diffusion of additional amounts of calcium from the surrounding fluids, which is in turn precipitated until the mass is solidly calcified. Wells objects to this hypothesis on the ground that the calcification would probably occur most markedly in the margin of the necrotic area, and lead to the formation of a solid wall of calcium which would hinder further osmotic flow and further deposition.

A theory which has been given great prominence is that there is formed in the necrotic area a substance or group of substances having a special affinity for calcium, the so-called "kalkfänger." The exact nature of these substances is not known, but it has been suggested that phosphoric acid, fatty acids and other substances may be of importance. To support the supposition that phosphoric acid plays a part is the fact that most of the calcium is found as phosphate, and that in the necrosis of tissues, nuclei are broken down and the resulting nucleoprotein may be transformed into phosphoric acid. There is no indication, however, that cartilage is especially rich in nucleoprotein. Wells implanted into the abdominal cavity of rabbits, tissues which had been killed by boiling, and found that those which were rich in nucleoprotein absorbed no more calcium than those which contained minimal amounts of nucleoprotein. There is little ground therefore for assuming that phosphoric acid attracts calcium in either normal or pathological calcification.

The occurrence of calcification in tubercles and in parts of blood vessels which exhibit fatty changes has given rise to the hypothesis that fatty acids play an important part in attracting calcium. The disintegration of fat leads to the formation of fatty acids and glycerol. The latter is probably absorbed and the former combine with calcium in the tissues to form calcium soaps. It is probable that the double decomposition of the calcium soaps in the presence of soluble phosphate and carbonate leads to the gradual transformation into calcium phosphate and carbonate in these areas. Klotz has made extensive studies in this field and comes to the conclusion that soaps are formed as a preliminary to calcification. His studies, however, were largely by the use of staining reactions in the tissues and not by quantitative chemical analysis. Wells and also Baldauf were unable to demonstrate by chemical methods the presence of soaps in any considerable amounts. At all stages of calcification the proportion of the salts of calcium found is constant. There is little doubt that the formation of soap plays some part, however, in the calcification of

fatty tumors and fat necrosis, but it is unlikely that this step is intermediate in the usual forms of pathological calcification.

At the present time it seems most likely that calcification is accomplished by physicochemical processes. Cartilage is a hyaline substance and takes up calcium readily. Elastic tissue in blood vessels has a special affinity for calcium. Hofmeister found that gelatin discs have an affinity for crystalloids in solution, including both calcium and iron. Wells has shown that there is no vital activity concerned in this phenomenon. Cartilage which had been killed by boiling, when implanted into the peritoneum, soon became thoroughly infiltrated with the various salts of calcium in essentially the same proportions as are found in bone and in pathological calcification. The continuity of the process of calcification in cartilage is believed by Hofmeister to be due to a decrease in carbon dioxide content of the cartilage. As the calcium passes through this tissue a decrease of carbon dioxide leads to precipitation; this leads to a restoration of the hyaline cartilage to a point where it may further take up calcium, and a continued or recurring decrease in carbon dioxide furthers the deposit of calcium. The belief in a progressive deposit of calcium in normal ossification and in pathological calcification, has been supported by the studies of Macklin. By periodic feeding of animals with madder he found that the calcium deposits showed madder staining during the period of feeding. The calcification which occurred between these periods was not stained by the dye. These experiments favor the view that the more or less periodic deposits of calcium in the tissues depend probably upon variation in the carbon dioxide content. It seems probable therefore, that calcification, whether pathologic or normal, depends upon a physicochemical condition of the necrotic substance or hyaline cartilage which attracts calcium and that the precipitation depends upon variation in carbon dioxide concentration in these parts.

Crystalline Deposits in Tissues.—Apart from the deposits of calcium which are principally in the form of granules rather than well defined crystals, the most common crystalline deposits are those of salts of uric acid. Uric acid and its salts are constantly present in the blood but the concentration is maintained at a low level by means of excretion through the kidneys. In gout and similar disturbances of metabolism, uric acid and its salts may accumulate in the blood in considerable amounts. They may then be deposited in crystalline form in cartilages, particularly those of the ear and of the joints, as well also as in the joint capsules and surrounding connective tissues. These deposits may lead to the formation of fairly large nodules which are spoken of as the gouty tophi. The kidneys of gout frequently show deposits of urates in the connective tissue of the pyramids. Microscopically, the urates are found in bundles of needle-like crystals surrounded as a rule by fibrous tissue, formed as the result of chronic inflammatory reaction of the tissues. It seems likely that the same physical condition which predisposes to the deposit of calcium, also predisposes to the deposit of urate, because the gouty deposits are found particularly in cartilage and in dense connective tissue.

On postmortem examination, the kidneys of very young infants frequently

show grossly in the pyramids radiating streaks of yellow, crystalline material. This is spoken of as *uric acid infarction* of the kidney. Microscopically, it is found to consist of deposits of crystals in small globules within the lumina of the collecting tubules. These are covered with a refractile colloidal substance. They are discharged into the pelvis of the kidney and excreted in the urine as a sandy material. Occasionally, they may serve as a centrum for the formation of calculi. The condition probably depends upon the altered metabolic condition incident to change from intra- to extra-uterine life. The material is usually uric acid and urates. The newborn excretes relatively larger amounts of uric acid than the adult. This is probably due to the liberation of nucleoprotein and the consequent formation of uric acid, dependent upon transformation of the erythrocytes from nucleated to non-nucleated forms, and also to the active destruction of leucocytes said to occur immediately after birth.

Cholesterol exists normally in the blood and in practically all body tissues. It is found in considerable amounts in the bile and in the adrenal cortex. Pathologically, it may be deposited in the tissues as a result of degeneration and of necrosis, particularly when these changes are associated with fatty metamorphosis of some kind. The crystals are found especially in the atheromatous plaques of arteriosclerosis as well as in certain chronic cysts. It is also found frequently in conditions where there is marked destruction of squamous epithelium, as for example, in sebaceous cysts of the skin, dermoid cysts and in the tumor known as cholesteatoma. If deposited in sufficient amounts, the white or yellowish-white glistening material is easily visible to the naked eye. Microscopically, the crystals are found in the form of colorless rhomboid plates with broken or re-entrant corners. The ordinary methods of fixing and embedding tissues dissolve and remove the crystals, so that in preparations of this sort there are simply found spaces representing the position formerly occupied by the cholesterol crystals. The formation of multinucleated giant cells, the so-called foreign body giant cells, is common about the crystals.

CONCREMENTS

Introduction.—Concrements or concretions are solid masses of material formed within hollow organs or passages in the body. They are variously made up of mineral, animal, or vegetable substances, the first two frequently mixed together. When they are sufficiently firm, as for example those made up almost entirely of mineral salts, they are called calculi or stones. Most concrements have a centrum, nidus or nucleus. The nidus may be a small clump of desquamated cells, a mass of mucin, a clump of bacteria, a small mass of fibrin or of leucocytes, a small scybalous mass of feces or a foreign body of some sort. Upon such a centrum, salts from the surrounding medium may be precipitated so as to form an encrustation, which gradually increases in size and forms the concrement. Certain concrements, however, are not formed in this way, as for example, the hair ball of the stomach which is made up of masses of swallowed hair. If these remain in the intestinal tract very long, they may

become infiltrated with carbonate and phosphate so as to form relatively solid concretions. The most common calculi of man are those found in the biliary and urinary tracts, but concretions are found in numerous other situations. Practically all forms of concretion are of considerable clinical importance.

Biliary Concrements.—These are found most often in the gall bladder, are frequent in the extrahepatic ducts and occasionally occur in the intrahepatic ducts. In the gall bladder they may be single or multiple. The single stones usually attain large size and have been found as large as the gall bladder itself. When there are few stones they are spheroidal, but when there are many they are faceted and pyramidal or polyhedral in shape. The edges of the facets are rounded. Frequently, calculi are associated with inflammations of the gall bladder. In some cases the inflammation may be primary, and, by virtue of the exudate and influences upon the bile, leads to the formation of calculi. In other instances the inflammation is secondary to the presence of calculi, which operate as foreign bodies to produce irritation and inflammation. Lodgment of a calculus in the cystic duct may produce marked distention of the duct and alteration of the contents of the gall bladder. Lodgment in the common duct may produce jaundice, absence of bile pigments in the stools, and if long continued, may lead to obstructive biliary cirrhosis of the liver. Inflammation of the gall bladder or the extrahepatic ducts, either with or without obstruction by stones, may result in multiple abscess formation in the liver or, if the infectious agent be not particularly virulent, or the resistance of the individual great, the sequence may be a chronic intrahepatic cholangitis.

THE CHEMICAL COMPOSITION of gall stones is varied. Practically all the elements which go to make up bile may enter into the composition of the calculi. Occasionally, calculi are found made up almost entirely of cholesterol. They are likely to have an organic nidus of some sort and a certain amount of organic stroma holding the calculus together. They are not very clearly stratified but show a yellowish-white or creamy-white glistening outer surface, and when incised the crystalline character of the cut surface is easily seen. The commoner stones are made up very largely of bile pigment. As to whether they are green or yellow depends upon the degree of oxidation of the pigment. These pigments are usually present not in pure form but as calcium combinations of the pigments. Occasionally, calculi are found made up entirely of pigment. The main constituent is bilirubin but there is in addition the simply oxidized biliverdin, the more oxidized bilifuscin and highly oxidized bilihumin. The more common gall bladder stones are usually distinctly laminated. In addition to the central nidus of organic material, there are found concentric and more or less alternating laminae made up of pigments and of cholesterol. As a rule, the pigmented layers predominate. Not infrequently when the gall bladder is the seat of inflammation, a previously formed calculus may serve as a nidus upon which there occurs a deposit of calcium salts. It is only rarely, however, that a pure calcium concrement is found in the biliary tract. Aschoff and Bacmeister classify gall stones as pure cholesterol stones, stratified cholesterol calcium stones, cholesteroid pigment calcium stones, composite stones com-

posed of cholesterol and a superficial incrustation of a mixture of cholesterol and calcium, bilirubin calcium stones which are the form found within the bile passages of the liver, and finally, calculi made of calcium carbonate.

THE MECHANISM OF THE FORMATION of gall stones has been extensively studied. The problem is directed toward the reasons for precipitation of the bile components, particularly as to the part played by variations in composition of the bile, variations in composition of body fluids generally, stagnation of bile, infection and disease of the gall bladder. Rous, and his coworkers, show that bile is concentrated in the gall bladder and it is at least possible that concentration may favor precipitation. Meltzer suggests that according to the law of contrary innervation, infrequent meals or starvation may induce stagnation of the bile and thus perhaps aid in precipitation. Rous, however, has shown that concrement formation may occur without stagnation, infection or gall bladder disease. Nevertheless, any of these factors may have some influence. The solubility of various components of the bile may change with concentration, but of greater importance probably are changes in hydrogen ion concentration. Lichtwitz points out also that the substances in solution in the bile are electronegative. It is therefore possible that the presence of protein, either in the form of a protein precipitate, in the form of a mass of mucus, or a mass of bacteria, all of which are electropositive, may determine the precipitation of these electronegative substances. As regards the body fluids generally, greatest attention has been directed toward their cholesterol content. Aschoff and Bacmeister claim that cholesterol deposit is primary in practically all concrements in the gall bladder. The cholesterol may be in excess due to a hypercholesterolemia, or may occur in the gall bladder as a result of degeneration of gall bladder epithelium. Chauffard also emphasizes the frequency of hypercholesterolemia in pregnancy, a state in which the first manifestations of cholelithiasis are likely to appear. Reimann and Magoun were unable to demonstrate hypercholesterolemia as at all constant in their cases of cholelithiasis, but it is possible, although in our opinion not necessarily probable, that hypercholesterolemia present at the moment of inception of the concrement may have disappeared by the time the disease became manifest. Certainly hypercholesterolemia is not a satisfactory clinical test for cholelithiasis. Nevertheless, experimentally induced hypercholesterolemia in animals appears to favor gall stone formation. Many patients give a history of infectious disease, and gall stones frequently contain organisms such as *bacillus typhosus*, *bacillus coli communis*, *streptococcus*, etc. On the other hand, many concrements are sterile. Aschoff and Bacmeister, on the ground that the concrements are permeable to bacteria, suggest that the presence of the organisms is secondary rather than primary.

A nidus or centrum is found in nearly all biliary concrements. Aufrecht believes that pigment masses formed in the smaller ducts may enter the gall bladder and serve as a nidus, but such masses are extremely rare in the smaller ducts. Rous and his colleagues find that in experimental animals the nidus is made up of calcium bilirubinate and carbonate upon an organic



PLATE IV—Various types of biliary calculi. *A*, Facetted pigment calculi. *B*, Facetted pigment calculi. *C*, Mulberry form of pigment calculi; upper figure shows cross section with nidus of pigment surrounded by layer of cholesterol and then a layer of pigment. *D*, Facetted pigment calculi covered with a layer of creamy white glistening cholesterol. *E*, Large solitary pigment calculus; encrusted with phosphates. *F*, Solitary pigment calculus showing in cross section multiple layers of pigment. *G*, Solitary calculus showing nidus of pigment radiating crystals of cholesterol and covering layer of pigment. *H*, Large facetted calculi; upper figure shows pigment nidus and multiple layers of pigment.

scaffolding. Such organic material may be the degenerative products or secretions of cells. Thus, it seems reasonable to assume in the light of our present knowledge that a nidus is provided by disease of the gall bladder or ducts, by infection, by ulceration, by exudate, perhaps by bacteria and perhaps by ordinary wear and tear of the cells. Precipitation may be determined by alterations of hydrogen ion concentration or by the nature of electrical charges, or perhaps by coarser changes in the composition of bile.

Urinary Concrements.—These usually are primary in the pelvis of the kidney but may originate in the urinary bladder; if found in the ureters they are practically always secondary to deposits in the renal pelvis. They are composed of materials derived from the urine, and usually are less varied in composition than are gall bladder stones. They are deposited as a result either of supersaturation of the urine with the constituents concerned, or of alteration in the composition of the urine. The centrum is more commonly a crystalline deposit than a mass of mucus or desquamated epithelial cells. In the urinary bladder the centrum is sometimes a foreign body introduced through the urethra. There is practically always a certain amount of organic material which binds the elements of the calculus together. The size and shape are variable. The calculi found in the renal pelvis are usually of markedly irregular shape, and if they attain sufficient size may form a cast of part, or of the whole, of the pelvis and its calices, which gives an irregularly stellate form. Calculi in the urinary bladder are usually spheroidal in shape. The color and consistence vary according to the composition of the calculus. Although the crystalloids of the urine are held in solution to a certain extent by the colloids, yet colloidal precipitation plays only a small part in the formation of urinary calculi. Fibrin, for example, occasionally is the centrum of a calculus. This is an irreversible colloid precipitate and is likely to produce disturbance in the colloidal balance of the urine. Urinary calculi may be made up of uric acid, of salts of uric acid, of oxalates, of phosphates, and certain other materials. Rarely do calculi consist of only one element, but urinary calculi more often than gall stones show great preponderance of a single substance.



FIG. 40—Uratc calculus from renal pelvis—the mulberry calculus.

CALCULI COMPOSED OF URIC ACID are fairly frequent. Uric acid is a relatively insoluble substance and is maintained in solution in the urine partly by virtue of the presence of sodium diphosphate and certain organic materials, particularly the urinary pigment. The margin between solubility and insolubility is so slight that not infrequently when the urine cools after excretion, sandy deposits of uric acid and urates may be thrown down. Uric acid is found in the urine combined chiefly with sodium, potassium and ammonium. Acidity of the urine, as is well known, is determined by the presence of acid phosphates. These possibly combine with the bases of the urate, thus liberating the uric acid which, on account of its greater insolubility, is precipitated. Such precipitation is favored

by concentration of uric acid in the blood and urine, a condition which may be caused by consuming food rich in nucleoproteins. Uric acid calculi are usually of brownish-red or reddish-yellow color, very hard, irregular in outline, often showing sharp points which may be a source of irritation to the renal pelvis, the ureter or the bladder. The color is due to the presence of urochrome and urobilin. Calculi composed of urates are more frequent in infancy than in later life, and are probably formed about a nucleus of urates which enters the renal pelvis when the salts constituting the common uric acid infarcts pass down the urinary tract. They are usually relatively soft and of brilliant yellow color. When found in adults they are usually secondary to infection of the urinary passages which leads to alkalinity of urine. In either case the calculi are most likely to be composed either of ammonium or sodium urate, but occasionally other salts may be found.

CONCREMENTS COMPOSED OF CALCIUM OXALATE are the most common calculi of the adult urinary tract. They are extremely hard, pale yellow, rough calculi which may not only irritate the mucous membrane but may also produce hemorrhage. Oxalic acid is a normal constituent of urine and is maintained in solution largely by reason of the presence of acid phosphates. Excessive ingestion of food containing oxalic acid such as rhubarb, spinach, grapes, may lead to supersaturation of this acid in the urine, which results in precipitation. Oxalic acid may be formed from uric acid in metabolism and may be produced in the urine by bacterial infection. The color depends upon the mixture of urinary pigment, but if hemorrhage has occurred, the calculi may assume a dark brown color due to hematogenous pigment.

CALCULI COMPOSED OF PHOSPHATES are usually secondary to the presence of other calculi which induce inflammation of the pelvis of the kidney or of the urinary bladder. Such inflammations are likely to be accompanied by decomposition, with the formation of ammonia from urea. This causes precipitation of several salts so that the calculi are composed largely of ammonium magnesium phosphate, with a certain amount of calcium phosphate, calcium oxalate and ammonium urate. In the renal pelvis they are practically always secondary to other calculi. In the bladder they may occasionally be primary, portions of desquamated epithelium from the bladder wall, mucus, pus cells, fibrin or other inflammatory products serving as a centrum. In fact, the deposit of phosphate in the urinary bladder may be so great as to form extensive encrustation of the bladder wall. The phosphatic calculi are usually grayish-white on the outer surface, although they too may be pigmented by urinary pigment or by blood pigment. The secondary calculi usually have a centrum composed of an oxalate or urate calculus. Phosphate calculi contain considerable organic material, which serves to bind the salts into a mass. These calculi are usually soft and friable.

Other urinary calculi are rare, but reports have appeared of calculi made up of cystine, xanthine, indican, fatty substances and cholesterol.

THE CONSEQUENCES OF CALCULI in the urinary tract may be serious. Lodging in a ureter, and occluding the tube, the stone interferes seriously with the function of the corresponding kidney. The result is great distention of the

renal pelvis, atrophy of kidney substance followed by fibrosis, and the complete conversion of the kidney and pelvis into a large cystic mass, showing little renal substance. If the stone lodge in the urethra, distention and hypertrophy of the urinary bladder may occur. In some cases the distention of the bladder may be so great as to induce rupture. In any situation in which these calculi lodge there is likely to be secondary infection, severe inflammation, not infrequently abscess formation and subsequent death from generalized infection. It is possible that calculi, particularly those composed of uric acid, may be dissolved in the body. The softer calculi, such as those composed almost entirely of phosphate, may undergo physical disintegration so that they may be discharged. It seems unlikely that treatment of any sort, except the breaking up of stones in the urinary bladder by mechanical means, may induce these favorable alterations.

Miscellaneous Concrements. Pancreatic and Salivary Calculi.—These are probably formed solely as the result of inflammatory disease of the ducts. Ligation of these ducts fails to lead to the production of calculi. Such calculi consist very largely of calcium phosphate. In the case of the pancreas, numerous other substances may be present, owing to the digestive effect of pancreatic juice upon the organic material in the duct wall and in the secretion itself. Certain pancreatic calculi are made up largely of calcium carbonate. Usually, however, there is a mixture of substances other than the main salt comprising the calculus. As a rule, these calculi are of considerable size, are granular on the outer surface, pale yellow or grayish-white in color, soft and easily broken up. One stone came under our observation which occupied the entire length of the pancreatic duct, and showed projections corresponding to the smaller divisions of the main duct. Calculi in the salivary glands similarly are made up of calcium salts and present the same general appearance. They are likely, however, to show more organic material binding the salts together. Sometimes salivary calculi are found to have a centrum of some foreign body such as a fragment of tooth, a piece of filling, or other foreign material.

Intestinal Concrements.—A variety of foreign bodies may serve as the centrum for calculus formation in the gastro-intestinal tract. These may be ingested foreign bodies such as pins, nails, fruit stones, pieces of bone, or foreign bodies which gain access in other ways, such as gall stones. Occasionally, hard masses of feces may remain in the intestine long enough to form the centrum of a calculus. As a rule, the intestinal calculi are made up very largely of ammonium magnesium phosphate, mixed sometimes with calcium salts, protein material and soaps. These calculi may occur in almost any part of the lower intestinal tract and may lead to partial or complete obstruction. Concrements of fecal material are not infrequently found in the appendix. They may have a nidus of some foreign body or may be composed entirely of feces. It is only rarely, however, that they are infiltrated to any considerable degree with mineral salts.

Other Forms of Concretions.—Occasionally concrements are found under the prepuce in cases of phimosis and apparently are the result of deposition of

urinary salts upon the accumulated smegma. Concrements are occasionally found in the prostate, originating in corpora amylacea upon which are deposited inorganic salts, particularly those of calcium, magnesium and phosphoric acid. Calculi are rarely found in the bronchi and sometimes may be expectorated. They are either deposits of lime salts and other materials upon a centrum of desquamated cells or exudate, or they represent calcified tuberculous masses which become extruded and lie in the bronchial tree. Foreign bodies in the nose sometimes lead to the deposit of calcium salts and the formation of the so-called rhinoliths. Such calculi may also form on a nidus of blood clot or nasal secretion. The necrotic material in the crypts of the tonsil may also occasionally serve as a nidus upon which salts of various kinds are deposited. Similar to these are the calcium deposits of sebaceous cysts of the skin, giving rise to the so-called cutaneous concretions.

Phleboliths or vein stones are usually more or less concentric deposits of lime upon and within blood clots in the veins. They are seen commonly in the splenic sinuses and occasionally in veins in other situations, notably the wall of the urinary bladder. Similar arterioliths are occasionally encountered.

Corpora Amylacea.—These bodies are found normally in the prostatic acini of adults. They occur in the lateral ventricles of the brain and in the meninges, and are not uncommon in chronic inflammation or hemorrhagic processes of the lung and in certain other situations. They are concentrically laminated bodies which take the acid stain and are visible only on microscopical examination. It is probable that their composition differs under different circumstances and in different locations. Inasmuch as some of these take the iodine stain and show metachromasia with methyl violet, it was long supposed that they were related to amyloid and hence the name was given. Ophüls points out that occasionally there occur concentrically laminated deposits of amyloid, but the study of corpora amylacea leads to the very definite conclusion that these bodies are not amyloid in nature. They apparently are harmless and lead to no inflammatory reaction on the part of the surrounding tissues. The centrum may be composed of small masses of cells, of protein precipitate, of mucin, or as in the central nervous system, may be myelin or fragments of neuroglia. Aside from the centrum, the structure of these bodies appears to be very largely protein, although it is probable that certain lipoids such as cholesterol and lecithin may be present. Very rarely such bodies in the prostate may lead to secondary deposits of calcium and the formation of prostatic concretions. In other situations the deposition of mineral salts is extremely rare. It is probable that the hyaline character of these bodies leads to an affinity for certain types of dyes, and for this reason there may be an absorption of iodine and a metachromatic reaction to methyl violet. They may even respond to the Best carmine stain although there is no likelihood that glycogen is present. Simmonds regards the corpora amylacea of the prostate as degeneration products, probably of desquamated epithelial cells with hyaline transformation. It is not clear how the laminated structure can be explained upon this hypothesis. It seems more likely that there is a repeated deposi-

tion of protein material from concentrated solutions, thrown down by physical alterations in the medium induced by the presence of some sort of nidus.

Psammmoma Bodies.—These are small bodies of concentrically laminated calcareous deposit, usually microscopic in size, but sometimes attaining a diameter of 2 or 3 millimeters. They are composed of carbonate and phosphate of calcium mixed with organic material. They are found particularly in connection with chronic inflammation and tumor formation, and are said by Piersol to be practically normal in the adult pineal gland in the form of the so-called "brain sand." Borst considers that the deposit of lime salts is usually upon a preëxisting hyaline matrix. They are not infrequent in chronic inflammations of the dura mater. They occur in both benign and malignant epithelial and connective tissues tumors, and such tumors are qualified as psammomatous. The true psammoma is a meningioma with numerous psammoma bodies. Grossly, the psammoma bodies can best be described as sand-like particles. Microscopically, they are generally spherical bodies, which show concentric lamellation of finely granular basophilic calcareous material.

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CHAPTER VI

ATROPHY

INTRODUCTION.

PHYSIOLOGICAL AND PATHOLOGICAL FORMS OF ATROPHY.
MORBID ANATOMY OF ATROPHY.

Introduction.—Atrophy is an acquired reduction in size of an organ or cell. It implies that the cell or organ or tissue has reached mature size before the reduction occurs, and is not to be confused with developmental defects such as agenesis, aplasia and hypoplasia. Agenesis usually signifies complete absence of an organ or tissue, due to some fault or deficiency of anlage. Aplasia refers to a failure of development to anything like mature size, although a mass of tissue, often merely of connective tissue, is found in the position of the organ. Hypoplasia indicates a failure of full development, the organ being well formed but congenitally small. In contrast, atrophy affects cells, tissues and organs which have gone through embryonal and fetal development, and have reached maturity commensurate with that of the body (see Mönckeberg). Naturally, hypoplastic organs may also be involved. Atrophy may affect the cells of an organ without reduction in its size, because of replacement by connective tissue, fat, or edematous fluid. It does not necessarily cause decreased function, because most organs have a reserve capacity sufficient to provide for considerable loss of organ substance. When atrophy goes beyond the compensating powers of reserve, functional deterioration becomes apparent.

Atrophy was formerly classified as simple, when the reduction in size was supposed to be due solely to decrease in the size of the cells, and numerical, when due to decrease in the number of cells. It is true that individual cells may be the seat of atrophy, and it is possible that this may be sufficiently extensive to reduce the size of the organ, but for all practical purposes any organ, the seat of a noteworthy atrophy, can be regarded as having suffered a loss of many of its cells. Consequently, numerical atrophy is used synonymously with atrophy when that term is referred to an organ or tissue.

The cause of atrophy is inadequate nutrition. This may be due to an excess of catabolism over anabolism, the result either of poor nutrition or of overwork, the so-called secondary atrophy. It may be due to some fault within the cell whereby its capacity for utilization of nutrition is decreased, or its growth energy inadequate, the so-called primary atrophy. It is often impossible to distinguish between these two forms of atrophy, and it is probable that the changes supposed to act in primary atrophy are partly if not largely responsible for all forms. The direct causes of atrophy are in many instances not sharply distinguished from those of degenerations, and atrophic cells are often the seat of other changes such as cloudy swelling and fatty degeneration.

Greene considers that a considerable amount of protein may be lost from muscle in the course of atrophy without real injury. Morse, studying atrophy

of the tadpole's tail, believes that the occlusion of blood vessels induces an acidity of the tissues, which favors autolysis. Bradley states that the changes in atrophy "are brought about by chemical liquefaction of the tissue proteins, catalyzed by enzymes present in the cells," and that the "same products are formed which appear as the end result of hydrolytic cleavage of protein by the digestive tract, namely, the peptides and amino-acids." Bradley fails to distinguish sharply between atrophy and necrosis, but his conclusions are apparently true in regard to both.

Provided the cause be removed, restoration of atrophic parts may readily take place. Severe degrees may be permanent and leave a shrunken fibrotic tissue or organ.

Atrophies are classified according to their more apparent and immediate causes, as considered in the paragraphs which follow.

Physiological atrophy is the normal and natural atrophy of certain tissues at certain age periods, as for example the atrophy of the thymus body at puberty, the atrophy of the ovary and breasts following the menopause. The lymph nodes usually show atrophy in late middle life or more advanced age. These may be due to a reduction of bioplastic energy. After pregnancy the uterine muscle undergoes reduction to normal, a process of comparative atrophy following the enlargement incident to pregnancy. Atrophy in tissues of old age is not to be regarded as purely physiological, for certain nutritional conditions appear here which may not be strictly normal.

Atrophy of Inanition.—The problems of inadequate nutrition have been studied as regards the entire body and parts of it. General inanition may be partial when food is taken in insufficient quantities, or complete when food is withheld entirely. Well nourished adults can withstand abstinence from food for several weeks provided water is given. The individual studied by Benedict lost one pound per day for thirty-one days, but little else of great significance was observed. Dogs have survived complete starvation for periods of seven weeks. Complete lack of food results in utilization of stored glycogen and fat, and may ultimately produce disturbance of general metabolism of these substances. Fixed acid intoxication by ketones may occur, but affects the obese more seriously than the lean. Starvation affects different parts of the body variously and the losses may result in abnormality of form. The central nervous system and to a lesser degree the bones are more resistant than other parts. Muscles which are in active use suffer less than those at rest. Jackson points out that cells are reduced in size, show a modified nucleus-cytoplasm ratio and resemble the embryonal type, but mitosis is usually inhibited. Subsequently cloudy swelling, fatty metamorphosis and death may occur. Slonaker and Card found in rats reduced growth, reduced reproductive capacity and increased death rate. Jackson refers certain abnormalities of form to inanition and suggests that in addition to effects on somatoplasm, the germ plasm may perhaps be so affected as to be of importance in heredity and evolution.

Undernutrition, as distinguished from starvation, probably differs only quantitatively in effect. It may be due to deficiency of all the food factors or

to deficiency of either carbohydrates, fats or proteins. It is especially significant as regards deficiencies of various vitamins, which may produce rickets, scurvy, etc. Undernutrition appears to be responsible for nutritional dropsy, although it is probable that the important feature is deficiency of proteins. How far it affects resistance to disease has not been fully ascertained, but Starling's investigation shows a great increase in the incidence of tuberculosis among the undernourished.

Aside from extrinsic conditions, atrophy of inanition may be caused by strictures of various parts of the alimentary canal, disease of digestive glands or obstruction to their ducts and other lesions, which either prevent the passage of food stuffs or interfere with their utilization.

Local interference with nutrition may be due to pressure or to partial occlusion of blood vessels. Such local atrophy is well illustrated in the arteriosclerotic kidney, where as the result of reduction in lumen of branches of the renal artery, the parenchyma undergoes atrophy. There is a replacement by connective tissue, which may contract to produce a scarred appearance.

Pressure Atrophy.—Prolonged pressure may produce atrophy of the compressed part. When the pressure is continuous, the atrophy proceeds more rapidly than when the pressure is interrupted, but even under the latter condition atrophy may be extreme. Pressure interferes with normal metabolic processes, probably because of interference with intake of nutrition and output of waste. Of great importance is the fact that there is compression of capillaries and small vessels, and even of large vessels so as to reduce circulation. These changes in circulation may, indeed, become so severe as to lead to necrosis. Bradley and Taylor believe that the interference with circulation leads to an asphyxia of the tissues, which produces increase of hydrogen ion concentration, and this in turn results in autolysis. Examples of pressure atrophy are frequent. Bed sores, or decubitus ulcers, represent the necrotic end product of atrophy of skin and tissues overlying the bony prominences, which are subject to prolonged pressure by long confinement to bed. It does not follow, however, that atrophy always results in necrosis or that the causes of atrophy and necrosis are identical. Sometimes children are born with depressed furrows in the skin and underlying tissues, due to pressure by fibrous bands of amnion or by the umbilical cord. Depending on the time the pressure originated, part of the process may be a hypoplasia due to interference with growth. The growth of tumors often leads to pressure atrophy of surrounding parts. This is well seen in tumor nodules in the liver, the liver cells showing reduction in size, and elongation due to the expansive pressure. The compressed cells sometimes show fat and even glycogen when there is little in other liver cells. MacCallum considers that these storage substances were in the cells when compressed, and that the interference with activity prevents their utilization, even although prolonged disease may exhaust the stores in the non-compressed cells. Occlusion of gland ducts may lead to accumulation of secretion at such high pressure as to produce atrophy of the parenchyma of the gland. This is well seen in occlusion of the ureter, following which the

renal pelvis may be markedly distended and the kidney markedly atrophic. The glomeruli resist atrophy longer than the parenchyma and there is usually considerable replacement by fibrous tissue. As in other glands, inactivity probably plays a part in this type of atrophy.

Atrophy from Inactivity.—Muscles rendered inactive by splints undergo moderate atrophy, but if the inactivity be due to motor paralysis, the atrophy may be especially marked. Interference with motor neurones may play a part in inhibiting the essential life processes of the cells. Extensive paralysis of a part may lead to atrophy of structures other than muscles, and in some cases the bony structures are atrophic and rarefied. Atrophy of certain glands, such as the pancreas, occurs after occlusion of the duct, but distention and appreciable pressure due to accumulated secretions do not necessarily occur, and the cause of the atrophy then is inactivity rather than pressure. As activity favors good circulation, so does inactivity favor poor circulation; and it seems probable that poor circulation must play a part in the atrophy of inactivity.

Toxic Atrophy.—Atrophy of various organs may appear in the course of infectious diseases, particularly if these be prolonged. Such forms of atrophy probably depend rather upon nutritional changes, incident to the infectious disease, than to true toxic action. Such diseases are likely to destroy erythrocytes and through this agency reduce nutrition. It is possible, however, that atrophy may occur in viscera secondary to the toxic degenerative changes which undoubtedly alter cellular metabolism. The fever of infectious disease leads to excess catabolism so that atrophy of cells is likely to be seen in prolonged febrile disease. The growth of malignant tumors may be accompanied by great wasting of the host. As has been mentioned above, tumors may interfere with assimilation of food so as to produce starvation atrophy, but numerous cases are accompanied by a condition called cachexia, which may interfere with cellular nutrition in the same general way as infectious fevers. This, however, is as yet problematic. Certain organs may show gross atrophy as the result of the influence of penetrating rays of light such as those of x-ray and radium. The reduction of size may be seen in genital glands and lymphoid apparatus, but is more largely due to destruction of cellular elements, as has been indicated in the discussion of necrosis, than to reduction in their size.

Neurotrophic Atrophy.—In discussing atrophy due to inactivity, neurotrophic influences were mentioned. The important involvement is that of motor nerves. It is maintained that nutrition depends to a certain extent upon the integrity of peripheral neurones, and that if these be destroyed the internal metabolism of the cells is so affected that they undergo atrophy. How great a part the neurotrophic disturbances play, as compared with the influence of inactivity and poor circulation, is problematical.

Atrophy from Overwork.—Provided nutrition be adequate, increased work leads to development of parts and to hypertrophy. There are limits to which hypertrophy may progress, and if the demand for work continue, atrophy may ensue. Examples are found in the atrophy in the arms of blacksmiths, and of the forearms in piano players, seamstresses, typists, etc. It is possible that

exhaustion of peripheral motor neurons plays an important part in the process, and that it is due as much to neurotrophic influences as to alterations in the muscles themselves. In many of these cases the atrophy is preceded by a period during which effort is accompanied by spasm of the muscle, the so-called occupational neuroses, such as writers' cramp, telegraphers' cramp, etc. Whether there is a primary nerve disturbance which leads to both cramp and atrophy, or whether the atrophy is due to exhaustion from the cramp, is not known. Possibly the atrophy of thyroid gland cells following hyperplasia and hypertrophy may be due to overwork.

Senile Atrophy.—It is well known that in the aged most of the organs undergo reduction in size. Atrophy is particularly noticeable in the skin, where reduction in the size of the papillæ of the corium produces a flat glossy, or satiny skin. It is difficult to state that these changes are an essential part of senility. The wear and tear of life with its numerous infections, improper diet, improper regulation of rest and exercise, alcohol and other drugs, probably play some part in the development of arteriosclerosis. Arteriosclerosis is not uncommon in young adult life and is practically constant in the aged. This vascular disease, particularly when it affects smaller vessels, leads directly to interference with blood flow, and the impoverished circulation which results therefrom certainly plays a large part in the atrophy of advanced life. Death, however, is a natural event. The growth stimulus furnished by fertilization of the ovum is gradually exhausted. It seems likely that associated with the growth stimulus is a capacity for maintenance of nutrition. Growth stimulus is depressed as mature stature is reached, but is evident throughout life in the reproduction of tissues destroyed in normal wear and tear. If age bring with it a reduction of growth stimulus and maintenance of nutrition, there must be, in senile atrophy, an indication of this exhaustion. Many animals exhibit the atrophy of old age without the vascular lesions that accompany senility in man. Adami regards senile atrophy as a physiological process, but it seems probable that in man it shows modifications in time of development, rate of progress and severity, due to the frequent presence of vascular and other diseases.

The Morphology of Atrophy.—In addition to reduction in size, organs the seat of atrophy show certain other changes. In a general way weight is reduced, but if the atrophy be moderate, and there be a considerable replacement of atrophic parenchymatous tissue by fibrous connective tissue, the weight may not be materially reduced and sometimes is found to be increased. The shape of the organ is retained except in those instances where the atrophy is due to pressure. Superficial changes, however, are not infrequent. The brain, when it undergoes atrophy is likely to show a reduction in the size of the gyri, accompanied by an increase in the width of the sulci. The liver is likely to show an increased sharpness of its edges. At times the atrophy may be so severe that the underlying structures may be easily apparent through the capsule. When replacement of atrophic parenchyma by connective tissue occurs, it is not uncommon for the connective tissue to undergo secondary contrac-

tion. This contraction may produce a nodular appearance of the outer surface, because of the contraction of masses of connective tissue between which the parenchymatous substance may bulge. The consistence of the organ is increased because of the fact that as the parenchymatous cells undergo atrophy, the connective tissue is relatively increased and, as has been indicated, is often absolutely increased. Because of the relative or absolute increase in connective tissue, the organ cuts with increased difficulty. The cut surface is likely to retract and may show changes due to the increase of connective tissue. As a rule, the blood content is about normal as is also moisture of the cut surface. Occasionally, however, especially when fat undergoes atrophy there may be some replacement by means of fluid, the so-called edema of atrophy. This, of course, produces moisture in the cut surface. Atrophy of voluntary muscles is not infrequently accompanied by partial replacement by fat. Under these circumstances the muscle may not be reduced in size, but is of reduced consistence, greasy, and shows the fat in cut section. The color of atrophic organs may not be altered from the normal. As has been pointed out, however, the atrophy of heart, liver and spleen, may be accompanied by relatively or absolutely increased amounts of pigment, giving grossly a brown appearance to the organs. Microscopically, pure atrophy of the cells shows simply reduction in their size. The shape is not altered except in cases of pressure atrophy where there is, in addition, condensation of the material within the cell membrane. The nuclei may be enlarged to give an increased nucleus-plasma ratio, but ultimately may be reduced in size. Storage substances such as fat and glycogen may remain in the atrophic cells, and because of the atrophy appear more prominent than is normally the case. Similarly, waste products may be apparent, such as lipid substances, myelin and pigments.

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CHAPTER VII

DISTURBANCES OF CIRCULATION

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Introduction.—The maintenance of circulation is essential to all normal bodily activities. Adequate circulation depends upon physical, chemical and biological factors, some well understood but many still the subject of investigation. A consideration of the varied activities of life, renders clear the fact that normal circulation is sufficient to meet extreme fluctuations in demand for work. This means that in the circulatory apparatus, as in other systems of the body, there is a large factor of reserve power or capacity for accommodation. Although several factors are concerned, the myocardium is responsible for much of the reserve power, which can be increased by systematic training to permit of physical labor far in excess of that possible for the untrained individual. The dynamic physiology of the circulation is concerned particularly with the heart, the blood and lymphatic vessels, and the constitution of the blood itself. Anatomical or physiological alterations of any of these important factors

may result in pathological disturbances. It must be understood, however, that the reserve power of the circulatory apparatus is so great that minor alterations may readily be compensated. Even marked disturbance of circulation may occur for a short period, to be followed by complete recovery and no apparent after effects. The common phenomenon of fainting, in which the circulation to the brain is so impaired as to cause loss of consciousness, is followed by no serious after effects. Athletes occasionally suffer with temporary acute dilatation of the heart and failure of circulation following undue muscular efforts. Unless frequently repeated, these disturbances apparently do no permanent damage.

Disturbances Due to the Heart.—In order to understand the variations in circulation observed in disease, it is necessary to have an adequate conception of the pathology of the heart, of its various appendages, of the circulatory apparatus as a whole. While the heart is the principal organ involved in the propulsion of blood, yet its activities are so intimately associated with those of the blood vessels, that a discussion of circulatory disturbances requires discussion of the circulatory system as a unit, as well as of its individual components. At the present time, it is advisable to give but a brief review of the conditions which lead to general circulatory disturbances, and then to consider the effect of general and local disturbances of the circulation upon the various viscera.

The heart is so constructed as to drive the blood against a certain degree of resistance, and is aided by the elasticity and perhaps the contractility of the large blood vessels, the flow of fluids through the tissues and lymphatics, the venous drainage and the pressure variations in the thorax during respiration. The myocardium contracts rhythmically, under the influence of its own inherent pacemaker and conduction system, as well as under the influence of the nervous system. Disease of the myocardium may be sufficient to interfere seriously with the power of contraction, so that it is unable to meet the demand of a normal amount of work, or the amount of work demanded may be in excess of the normal capacity of the myocardium. Either of these circumstances leads to failure of the myocardium to perform its work. Failure of the myocardium due to an excessive demand for work is spoken of as passive, whereas that due to disease of the myocardium itself is referred to as active. If either type of failure go beyond the point of circulatory compensation by peripheral constriction and increased resistance, the arterial blood pressure falls and general disturbances of circulation appear. It is generally considered that the opening and closing of the valves is essential to the normal activity of the heart, but it is also well known that minor alterations in the anatomy of the valves may lead to no important or perceptible disturbance of circulation. The valves of the heart may be the seat of malformation arising in embryonic life; they may be the seat of acute inflammation, chronic inflammation, or of a fibrotic process similar to that of arteriosclerosis. The connective tissue rings of the valves are, in all probability, supported to a considerable degree by the cardiac muscle, and if this fail the ring may dilate. The rings may also dilate as the result of disease within themselves. Minor embryological mal-

formation of the valves, such as four leaflets in the semilunar valves or minor fenestrations, apparently do no damage, but other malformations may be sufficiently serious to alter circulation markedly. It is also probable that the existence of congenital malformation predisposes to subsequent disease of the valves. The growth of vegetations or the stiffening or adhesion of leaflets, may prevent their proper opening and thus obstruct blood flow. The partial destruction, retraction or adhesion of valve leaflets, or dilatation of the ring results in failure to close, or insufficiency, which permits regurgitation or back flow through the orifice. As the result of these processes, there is an increased demand for muscular work. Contraction of valve rings, stiffening of leaflets or adhesion of leaflets to one another, may so constrict the orifice as to lead to obstruction to outflow of blood and thus necessitate increased work on the part of the propelling chamber. Although, in acute disease of the valves, it may be possible for vegetations to accumulate so rapidly as to cause dilatation of the chamber or chambers concerned, it is our opinion that vegetations of any considerable size require several days for formation, and it is certain that the more marked deformities of chronic valvular disease require weeks, months or years, for full development. In the stage of minor deformity, the reserve power of the myocardium compensates functionally, but as time goes on and the general condition progresses favorably, the continued demand for extra work results in hypertrophy of the muscle. The chamber affected by the valvular fault undergoes hypertrophy, but the hypertrophy also affects to a lesser degree the entire myocardium. This is largely because the spiral arrangement of the cardiac muscle renders the heart a muscular unit. Failure of one chamber may lead to accumulation of blood in other chambers and thus produce an extension of the hypertrophy. The pericardium also plays a part in normal circulation. The parietal pericardium is not easily distensible and if the sac be filled with fluid, the intrapericardial pressure may prevent filling of the heart chambers by limiting the diastolic expansion of the chamber, and by compressing the veins entering the atria. If on the other hand the sac be partly or completely obliterated by fibrous adhesions, systolic contraction must be more forceful than normal and hypertrophy results. The development of hypertrophy depends upon the demand for increased work, the provision of adequate nutrition, and the capacity of the heart muscle to take up the extra nutrition. In chronic valvular and pericardial lesions, the demand for increased work is permanent. The hypertrophy of the muscle cannot go on indefinitely increasing and reaches a point where nutrition of the muscle is inadequate for further growth. As the hypertrophy increases and the nutrition becomes relatively decreased, the reserve power of the heart is not proportionately as great as in the normal organ. A myocardium in this condition cannot readily meet further demands for work, and is especially susceptible to toxic or infective influences. If these accidents intervene, the organ is unable to carry on its work, the chambers dilate, the circulation of blood is interfered with, and the heart is said to be in a state of decompensation, or congestive failure. The rhythmic contraction of the heart is an essential of normal circulation.

Arrhythmia may be caused by disturbance of the nervous control of the heart, of the pacemaker and conduction system, and of the contracting muscle. Arrhythmias, however, may proceed for a long time without obvious disturbance of circulation except during increased bodily activity. Further discussion is to be found in the chapter on the cardiovascular system.

Disturbances Originating in the Vascular System.—The vascular system contributes its part to circulation by virtue of its elasticity and contractility. The elasticity takes up the rush of blood as it comes from the heart and favors the onward flow of this fluid. Contractility plays a part in equalization of blood flow to the various parts of the body, and in the larger vessels probably also contributes to the onward flow of the blood. With the possible exception of the musculature of very small vessels, the contractility of the vascular tree is under the influence of nerves, which control the tension of the vascular walls and the resistance to circulation. This resistance together with the drive of the heart produces the hydraulic pressure of blood in the vessels. The activity of vasomotor nerves provides for equalization of circulation. Internal secretions, particularly that of the adrenals, probably also aid in the maintenance of circulation. Temporary increases of vascular tonus may result from the stimulation of vasomotor nerves as, for example, in asphyxia, in psychic disturbances and following the use of certain poisons such as alcohol and strychnine. Provided the heart be adequate, these disturbances may be so met as to result in very little disturbance in the onflow of blood. Prolonged hypertension causes hypertrophy of the heart, which, as has been pointed out above, may be followed by a decompensation and corresponding failure of circulation; but as long as the heart compensates, circulation is almost, if not quite, normal. Decreases of blood pressure may be due to disturbances of the vasomotor centers such as are produced by bacterial poisons. Acute infectious diseases such as diphtheria, typhoid fever, pneumonia and others may, in the more advanced stages, be accompanied by low blood pressure. Chronic wasting diseases, such as tuberculosis and malignant tumors, certain cases of congenital vascular and cardiac hypoplasia, and the curious syndrome called Addison's disease are accompanied by low blood pressure. Ingested poisons may also lead to low blood pressure as for example, large amounts of alcohol, chloral hydrate and the cyanides. Hemorrhage may be so excessive as to go beyond the compensating effects of vasoconstriction and produce low blood pressure. Operative and wound shock may result in marked fall in blood pressure. Crile has conducted extensive studies of the mechanism of shock, but his proposition that the essential cause is exhaustion of nerve cells has been widely opposed. Porter, studying wound shock, came to the conclusion that fat embolism is the cause, but the work of Wiggers, Simonds, Warthin and others shows that shock and fat embolism differ both physiologically and anatomically. A vast literature has accumulated on this subject, but as yet the primary cause or causes are not clearly understood. Accumulation of blood in the vessels of the abdominal cavity often leads to general reduction in blood pressure. This accumulation may be found in shock, it may be seen in acute peritonitis and

possibly occurs as the result of psychic disturbance. Anaphylactic shock and intravenous injections of a wide variety of colloids and crystalloids may produce a fall of systemic pressure. Low blood pressure results in failure in onward drive of the blood, failure to supply nutrition and oxygen, and failure to provide fluid for tissue circulation. Removal of the vis a tergo may lead to marked stasis of venous circulation.

In order to maintain normal relations of circulation, the volume output of both ventricles must be the same. Hence, the pulmonary circulation plays an important part in regulation of the greater circulation and vice versa. This lesser circulation is maintained by the activity of the right heart, and to a certain extent by the movement of the thorax. The vessels in the pulmonary circuit alter their size according to different conditions, but in a discussion as to whether or not this alteration of size is reflex, Wiggers concludes that the demonstration of reflex vasomotor effects on the pulmonary circulation, must be regarded as probable rather than established. Certain diseases may interfere with pulmonary circulation, such as chronic fibrous tuberculosis, chronic emphysema, fluid or tumors in the pleura, alteration of motility of the chest wall and numerous other conditions. For a time these are compensated for by hypertrophy of the right heart, but when this reaches its limit the blood accumulates in the right ventricle, then in the right atrium and then in the general venous circulation. If circumstances arise which determine an increased output on the part of the right ventricle, the pulmonary vessels take up the circulation and pass it on to the left atrium and left ventricle, where the increased amount of blood stimulates the left ventricle to increased effort. This is in accord with the general law that increased tension or stretching of muscle leads immediately to increased contraction. If, however, the left ventricle through disease of the muscle or of the valves, be unable to take care of this increased amount of blood, pulmonary hyperemia ensues.

Disturbances Due to Mass and Constitution of Blood.—The determination of the volume of blood in the animal body depends upon methods which, according to Erlanger, are subject to factors of error which cannot be entirely corrected in the calculations. Various methods give blood volume ranging between 4.8 per cent. and 9.8 per cent. of the body weight with an average of 7.6 per cent. Many investigators have regarded the blood volume as one of the physiological constants of the body, but Barcroft states that it is a "physiological variable which is adjusted to the work required of it and to the size of the bed it occupies." There is no doubt that reduction in the volume of blood by accidental means may, up to certain limits, be restored by withdrawal of fluid from the tissues, and Lamson maintains that there are also storage places for red blood corpuscles which may be called upon for replacement. On the other hand, the tissues take up excesses of fluid in the blood stream. Bogert, Underhill and Mendel found that fluid equivalent to the calculated total amount of blood in the body, when injected into the circulation, was removed within thirty minutes, and that in the rabbit the tissues are capable of taking up fluid equal to approximately four times the volume

of blood in the body. Although it is undoubtedly true that colloids may pass through vessel walls, yet according to the work of Bayliss and others the colloidal condition of the blood is important in maintaining volume. Crystalloids also play a part in the regulation of body fluids. Whether this has an influence on the actual volume of the blood is a matter of question. The ingestion of salt leads to a retention of body fluid, but it is probable that this is accumulated almost entirely in the tissues. In the presence of experimental forms of nephrosis, the introduction of large amounts of fluids in the circulation is not compensated for as quickly as under normal conditions. In man, however, this failure of excretion of fluid appears to show itself particularly in accumulation of the fluid in the tissues in the form of edema.

Pathological alterations in blood volume occur under a variety of circumstances. These are classified as increases and decreases; the former called plethora, the latter called anemia. True plethora signifies an increase in the corpuscles and plasma of the blood and is well exemplified in the syndrome known as Vaquez-Osler disease. The syndrome includes plethora, cyanosis, enlarged spleen, and attacks of unconsciousness. In contrast to this occurs hydremic plethora in which the absolute number of corpuscles is approximately normal, but the fluid of the blood is increased. This occurs, according to Plesch, as a result of diseases of the kidney accompanied by edema, but may be found without edema. The increase of fluid depends partly upon decreased secretion and partly upon increased osmotic pressure of the blood. Temporary hydremic plethora may result from excessive ingestion of fluid, but only during the short period which normally elapses before the fluid is entirely removed from the blood. The ingestion of fluid may be so great and so continuous, however, as to maintain a practically constant increased volume of blood. Hydremic plethora differs from hydremia, in that the former is an increase in the amount of fluid in the blood with an increase in the absolute volume, whereas the latter is a relative increase in the amount of fluid, without increase in the total volume. Hydremia is seen particularly following hemorrhage where the lost volume of blood is replaced by fluid from the tissues. It is likely also to accompany a number of wasting diseases.

Decreases in the volume of blood are referred to as anemia or oligemia. These terms refer particularly to loss of corpuscular elements for, as has been indicated, losses of blood are easily compensated for in volume by withdrawal of fluid from the tissues. The restoration of corpuscles occurs much more slowly, occupying ten days or more. Observation of donors for transfusion shows that losses of from 500 to 1000 cc. can be well borne by a normal individual. Exactly how much can be withstood by man, without fatal results, is not definitely known, but in animals losses of two-thirds of the entire blood volume may be survived. The loss of corpuscles may result from a single hemorrhage, frequently repeated small hemorrhages, or disease of the hematopoietic system. The term anhydremia signifies loss of the fluid part of the blood, and is seen particularly in connection with severe watery diarrhea such as cholera. Unless prolonged and severe, such losses of fluid can readily be replaced.

In animals, Beck and Holman have shown that the heart accomodates its size to variations in the quantity of circulating fluid, and Eyster and Middleton have demonstrated in man a reduction in size of the heart immediately following withdrawal of as little as 500 cc. of blood from the circulation. The blood pressure and pulse pressure are likely to fall following withdrawal of blood and rise following injections of blood. These changes are not permanent because the bulk of fluid soon returns to or about normal.

The viscosity of the blood is maintained largely by virtue of the corpuscles but is contributed to by the gases, particularly carbon dioxide, the crystalloids and the colloids of the plasma. The principle factor in altering the viscosity of the blood is the content of carbon dioxide. Hence, when prolonged passive hyperemia exists, and oxygenation of the blood is reduced by slow or deficient circulation through the lungs, viscosity may materially increase. This is compensated for to a certain degree by the dilatation of peripheral vessels. The increase of viscosity, due to an absolute increase in the number of corpuscles, such as seen in true plethora, as well as the relative increase incident to anhydremia, is compensated for in the same manner.

Summary.—All the conditions enumerated above influence the circulation of the blood, but it is undoubtedly true that some are of much more importance than are others. Failure of the myocardium is of the utmost importance in general circulatory failure. It leads to inadequate drive from the heart and therefore to an insufficiency of the circulation. When valvular disease is present, the stage of decompensation leads to the same general effect. Alterations of the vascular system, whether temporary or permanent, as in disease and old age, certainly produce alteration of blood flow, and these may result secondarily in disease of the heart, which in the stage of decompensation gives rise to serious disturbance. Increases in the mass of blood to be moved, as well as increases of viscosity, have essentially the same effect on circulation as increased resistance. Decreases in the volume and number of corpuscles in the blood reduce the momentum and theoretically increase the work of the heart. That these decreases in themselves produce serious disturbances is open to considerable doubt. In profound anemias, the disturbance of circulation appears to be due rather to deficient nutrition provided to the myocardium by the inadequate food and oxygen supply, than to the direct effect of lowering of specific gravity or of decreasing the absolute amount of blood to be pumped by the heart. The ultimate result of practically all these disturbances is passive hyperemia and this will be discussed under its own heading.

Local Circulatory Disturbances.—In a general way, circulatory disturbance results in either an increase of blood to a part or a decrease of blood to a part. An increased volume of blood to a part is referred to as congestion or hyperemia. These increases may be supplied on the part of the arterial system or may result from accumulation of blood in the venous system. Decrease of blood to a part is called local anemia or ischemia.

Arterial or Active Hyperemia.—Hyperemia of organs occurs under physiological circumstances. The pregnant uterus contains more blood in proportion

to its volume than does the quiescent uterus, and the same is true of the functioning breast. Numerous glandular and other structures show an increased blood content during activity. This increased blood content is found to reside very largely in an increased calibre of the smaller arterioles and arteriolar capillaries. Whether or not this is due to reflex activity is problematical. It is known that alkalis cause a contraction of vascular muscle, and that acids produce a dilatation of the vessels due to atonic relaxation of vascular muscle. Gaskell suggests that the decreased alkalinity of the fluid flowing away from the functionally active parts, results in relaxation of vascular muscle, thereby providing for the active hyperemia. There is no doubt, however, that under certain circumstances reflex activity has something to do with active hyperemia. This is seen in emotional conditions accompanied by flushing of the skin. Direct irritation of the skin as well as increases of temperature of the skin surface also lead to active hyperemia of that part. Pathologically, the most important form of active hyperemia is that which accompanies inflammation. This is the first stage of the process of inflammation and its mechanism will be discussed in the consideration of that topic. There are other forms of active hyperemia that may be referred to as irritative, because they probably result from stimulation of the vasodilators. Included in this group are the local erythemas resulting from ingestion of food to which the patient is especially susceptible, such as seafoods, strawberries, eggs and other substances, as well as certain drugs, such as quinine. Local hyperemia may accompany neuralgia and is seen in various forms of herpes. Neuroparalytic hyperemia is the result of interruption of stimuli through the vasoconstrictors. This is particularly well exemplified in destructive lesions of the cervical sympathetic nerves by wounds, by disease of the vertebræ, invading tumors, or inflammation in the neighborhood. Hyperemia of the side of the face and of the neck, sometimes with profuse sweating, dilatation of pupil and drooping of eyelid are observed on the side affected. The so-called reflex hyperemias are in part physiological and in part pathological. Probably of reflex origin is the active dilatation of vessels in the interior of the body following external chilling. It is probable also that the flushing of the skin during emotion is of reflex origin. It must undoubtedly be true that serious disease of the vessel walls may lead to arterial dilatation, but this is probably not to be regarded as active hyperemia.

Morphology of Active Hyperemia.—An organ or part the seat of arterial or active hyperemia is of bright red color, but slight pressure will force the blood out so that the part becomes pallid. By fine examination, provided the covering membranes are not too thick, it is possible to see the smaller vessels distended and pulsating. If the hyperemia be sufficiently severe the organ may be tense. There is usually some swelling, and both objectively and subjectively, an increase in temperature when hyperemia is on or near the surface of the body. Microscopic observations are best made in living objects, because after death the blood sinks rapidly out of the part and the hyperemia may not be visible. Exception to this is found in acute inflammation where certain secondary changes preserve the calibre of the vessels as in life. Active hyper-

emia may be apparent in life as in the rashes of scarlet fever and measles, but after death these rapidly disappear and histologic examination may show little or no vascular change. Edema, wandering out of blood cells and other phenomena occurring in passive hyperemia, such as will be described subsequently, are not to be found in simple active hyperemia. When disease of the smaller vessels or a deterioration of the vessels, such as is seen in old age complicates the hyperemia, small hemorrhages may occur. Diagnosis of active hyperemia at autopsy is usually postulated only in those cases where infection or inflammation is known to be present. With-

out some such condition it is practically impossible to differentiate active from passive hyperemia after death.

Venous or Passive Hyperemia.—

The accumulation of blood in the venous and venous-capillary side of the circulation is one of the commonest findings at autopsy, and is one of the most important sequences of chronic heart, lung and liver disease. This condition results from interference with the passage of blood through the veins, is therefore secondary to other changes, and is commonly referred to as passive hyperemia. It varies between a very slight or moderate damming back of the blood in the venous circulation to complete cessation or stasis. The maintenance of venous circulation depends in part upon the pressure of blood transmitted through the capillaries to the venous circulation, the so-called *vis a tergo*. The flow is maintained by muscular contraction, patency of the venous channels,

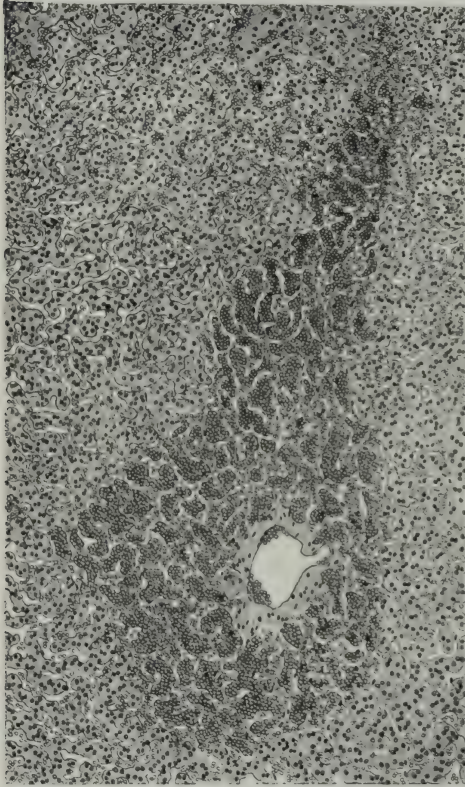


FIG. 41—Passive hyperemia of liver, showing the accumulation of blood in the central sinusoids and distention of central vein.

proper function of valves of the veins, suction of the thorax and integrity of the valves in the heart. It will therefore be seen that damming back of the blood in the circulation may occur by disturbance of any of these elements. Practically speaking, however, the pressure transmitted from the arterial side of the circulation to the capillaries is of relatively little significance. The appearance of a general passive hyperemia due to a decrease in arterial pressure, is dependent mainly upon failure of the myocardium which simultaneously causes the passive hyperemia. Under these circumstances the output of blood from the left ventricle is reduced in amount; this occasions a certain amount of extra filling of the atrium, a damming

back in the pulmonary circuit, right ventricle, right atrium and a resultant accumulation of blood in the systemic veins. Diseases of valves of the heart, if not compensated by the myocardium, may result in a similar cycle and consequent venous engorgement. In fact, any condition which results in decreased systolic output of the heart, whether it be the result of accumulation of fluid in the pericardium, tumors in various situations, chronic diseases of the myocardium, or disease of the valves, may result in passive hyperemia. Failure of muscular activity to propel the blood through the veins may be of little significance in so far as general hyperemia is concerned, but it is probable that extensive local disturbance may occur, such as the development of varicose veins of the leg, from lack of sufficient exercise to propel the blood. The same may be true of dilatation of other veins, as for example those of the spermatic cord and of the lower end of the rectum. With distension of veins by passive hyperemia their valves become insufficient, fail both to support the column of blood and to aid in its movement. Conditions which limit the respiratory movements, especially inspiration, may decrease the amount of negative pressure within the chest and thus impair one factor in maintaining the venous blood flow. Among such conditions are chronic fibrous diseases of the lungs, emphysema, and certain diseases of the pleura such as extensive fibrosis, fluid in the sac, or tumors. In these instances the passive hyperemia depends not alone on decrease of suction, for the diseases leading to this decrease are commonly associated with chronic diseases of the lungs, heart, pericardium or other organs. Chronic diseases of the lungs, by virtue of fibrosis and stiffening of the organs, may lead to increased resistance to pulmonary circulation, which ultimately causes a decreased systolic output from the right ventricle; this results in accumulation of blood in the right atrium and thence in the systemic veins. Cirrhosis of the liver is an important cause of passive hyperemia in the abdominal viscera. It is generally believed that the abdominal hyperemia is due to reduction in the size of the portal veins within the liver by reason of fibrosis.

In addition to these more general causes, there are numerous causes for local passive hyperemia referable to narrowing of the lumen of veins. This reduction in lumen may result from disease within the vein such as thrombosis or thrombophlebitis, disease in the vein wall such as phlebosclerosis, or from pressure upon the vein from without. Passive hyperemia due to local causes, where the circulation is dammed back in only a limited area, may be somewhat ameliorated by the establishment of collateral circulation. The passive hyperemia of a lower extremity, resulting from thrombosis of a femoral vein, may not lead to long standing or extensive hyperemia because of collateral circulation established in the deeper veins. In the same general manner the hyperemia of the abdominal viscera, incident to cirrhosis of the liver, may be compensated for by the collateral circulation, established through the lower abdominal veins connecting with superficial veins of the abdominal wall. The veins which thus serve as collaterals usually enlarge in order to carry the increased blood flow. The lymphatic vessels, which drain the affected part, also enlarge to take care of the added fluid formed as the result of the passive hyperemia.

Morphology of Passive Hyperemia.—The accumulation of venous blood in a part gives to it a dark red or bluish-red color. Affecting the skin and underlying tissues, this is referred to as cyanosis (see Lundsgaard and Van Slyke). Organs the seat of passive hyperemia are likely to be somewhat increased in size and if encapsulated the capsule is tense. The weight and consistency are increased. Upon death or removal from the body, the blood may drain out of the organ in considerable amounts, so that the weight may be reduced below that which existed in life. Hyperemic organs removed by surgical operation may lose one-third of the weight or more by bleeding, as soon as the organ is cut open. Even after this loss of weight the dark red or purple color persists. The cut surface bleeds freely. In the liver, the bleeding from the central zones of the lobules results in retraction of those portions so that they are on a lower level in the cut surface than the peripheral zones. Microscopically the veins, venules and venous capillaries are found engorged with blood. A simple, un-

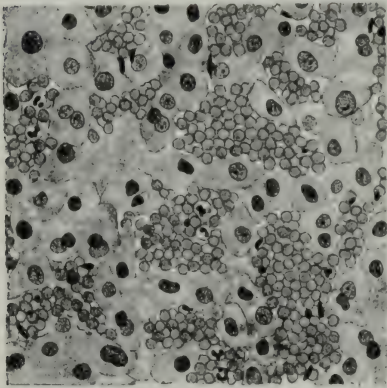


FIG. 42—Higher magnification of a field of FIG. 41, showing sinusoids distended with blood.

complicated picture of passive hyperemia is rarely seen because secondary changes soon occur. The decreased circulation, incident to passive hyperemia, leads to impoverished nutrition of the part concerned. The degenerative changes secondary to depraved nutrition are therefore likely to be seen, and these include cloudy swelling, fatty degeneration, atrophy and necrosis. The more severe or the more prolonged the passive hyperemia, the more pronounced are these degenerative disturbances. They lead to important functional disturbances in certain areas. For example, the degeneration in the gastro-intestinal glands may

lead to severe digestive disturbance; in the kidney, functional deficiencies of excretion are often produced; in the liver, the reserve power may be so great that no functional alteration can be demonstrated. The deterioration of tissues may involve the walls of the venules and capillaries to such a degree that hemorrhage occurs. In passive hyperemia of the lung, for example, it is not at all uncommon for patients to expectorate sputum stained by the incident hemorrhage. The deterioration affects not only the tissue cells but also the blood corpuscles themselves, especially those that have become extravasated, so that in cases of prolonged hyperemia, hematogenous pigmentation of the tissues is likely to be marked. In the liver the pigment is found in the parenchymatous cells near the center of the lobules. In other viscera the pigment is likely to be found in endotheliocytes in the neighborhood of the hyperemic vessels. This is likely to be easily demonstrable in the spleen, and is also seen in the lung, where the endotheliocytes filled with blood pigment appear both within the alveoli, in the infundibula, within the lymphatic spaces and other structures. In the kidney the pigment may be found in the

epithelial cells of the tubules but is not commonly observed. Pigment may also be found in extracellular positions.

A frequent accompaniment of passive hyperemia is EDEMA. This term signifies the accumulation of fluid in the tissues or in body spaces. Edema occurs also as a part of certain forms of kidney disease, as the result of inflammation, in certain curious nervous conditions such as angioneurotic edema, and in severe and prolonged disturbances of nutrition such as "war dropsy" or nutritional edema, etc. McLean emphasizes the importance of the conception of the body fluids as a problem of regulation of volume, and regards edema as a "quantitative rather than a qualitative deviation from the normal." Edema of various forms will be discussed in the chapters on systemic pathology and consideration will be given here to cardiac edema. As Loeb points out, cardiac edema is in part dependent upon vascular dilatation, especially of venules and capillaries, associated with slowing of the current.

This causes increased transudation of tissue fluids and decreased absorption. There is probably an increased permeability of capillary walls with passage outward of water and salt, but that this is due to injury of the vessel walls is not proven. It has been thought that hydremic plethora accentuates the vascular phenomena, but studies of this condition in cardiac edema have been contradictory. Failure of proper drainage may lead to accumulation in the tissues of crystalloids, which by raising the osmotic pressure will draw fluid from the vessels. The decrease in circulation causes poor oxidation of the tissues, which according to M. H. Fischer

results in accumulation of acids in the tissues. The combination of acid with protein results in the formation of a hydrophilic colloid, which attracts water from the vessels. In the general passive hyperemia of cardiac disease, the pressure in the subclavian vein may be sufficient to interfere with the drainage of lymph from the thoracic duct, and thus aid in the production of edema in abdomen and thorax. General passive hyperemia may induce lesions of the kidney, but unless these be severe, renal insufficiency does not contribute to cardiac edema. However, the causes of endocarditis not infrequently also lead to nephritis, and the edema of cardiac failure in these cases may be accentuated by edema of renal origin. McLean points out that as a result of cardiac insufficiency, there is a tendency to increase of the general fluid volume, which however, is usually compensated for by regulatory mechanisms except in dependent parts of the body, where "gravity becomes the determining factor."

The constitution of edematous fluids varies with the cause and with the situation of the fluid, but that which appears as the result of passive hyperemia

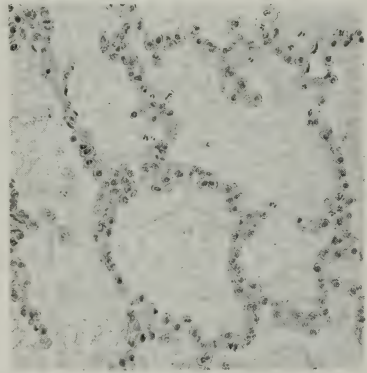


FIG. 43—Edema of pulmonary alveoli. The fluid has been precipitated by preparation and appears as granular material in the alveoli.

is a thin, watery fluid, poor in protein and in salts and contains but few cells. It is referred to as a transudate, in contradistinction to the edema of inflammation which is referred to as an exudate. Tissues the seat of edema are swollen, boggy, of doughy consistence, and when pressed leave the imprint of the finger. The area is more or less pallid, depending upon the degree of associated passive hyperemia. Incision releases the fluid and these characters are thereafter less marked. The cut surface is pale, semitransparent or gelatinous, and from it can be expressed a thin, limpid, colorless or blood-tinged, salmon-colored fluid. In the serous cavities such as pleura, pericardium and peritoneum, fluid is normally present, and edema is said to be present when the amount of fluid found is materially in excess of the normal. Histological examination of edematous tissues, shows the essential tissue elements separated from one another by the fluid accumulation. In stained specimens the spaces thus formed are occupied by fine, acidophilic granules due to precipitation of the protein content of the fluid. Accordingly, the number and size of the granules vary with the protein content. Over-heating of specimens in their preparation may produce similar separation of fixed tissue elements, but the acidophilic precipitate is absent.

As passive hyperemia becomes prolonged, an additional sequence is the formation of fibrous connective tissue. This deposition of connective tissue signifies *chronicity of the process*. The exact reason for its development is not clearly known but several possibilities may be considered. As has been pointed out in the discussion of atrophy, the reduction in amount of parenchymatous tissue leads to its replacement by connective tissue, and it is possible that the atrophy incident to passive hyperemia, may induce similar replacement fibrosis. The metabolic changes in tissues, the seat of passive hyperemia, may be the cause of accumulation of irritants of toxic nature, and it is well known that prolonged, low grade irritation in any situation is likely to lead to fibrosis. It is also thought that prolonged edema may stimulate fibrosis. Fibrosis leads to increased density and firmness of the tissue affected, and may ultimately result in shrinking due to contraction of the connective tissue. Microscopically the fibrosis is found particularly in the neighborhood of the hyperemic vessels. In the kidney it is likely to be found in glomeruli and around the smaller vessels of the cortex and medulla. In the liver it is seen around the central veins. In the lungs it appears about the smaller vascular trunks and the capillaries of the alveolar walls. The fact that in the spleen the fibrosis is diffuse, affecting the interstitial tissue near the sinusoids as well as the connective tissue of the trabeculæ, leads one to believe that irritation of accumulated toxic products incident to passive hyperemia, may result in the fibrosis, because in the spleen there is no true parenchymatous tissue and until passive hyperemia is very marked there is likely to be no atrophy. In generalizing the results found in various organs, it would seem probable that atrophy as well as degeneration and the irritative effects of toxic products, all lead to the fibrosis. Veins not within organs, such as those of the extremities, usually become elongated as the prolonged, increased intravenous pressure reduces their elasticity. Elongation

produces tortuosity and the same factors which produce fibrosis in tissues lead to fibrosis of the vein walls. These are varicose veins. Similar changes occur in tributary lymphatics. These are not likely to become tortuous, but exhibit dilatation and fibrosis.

ACTUAL STASIS OF BLOOD in the vessels, which means complete cessation of current, may be the result of complete occlusion of the vessel. It appears in the margins of ulcers and old wounds, apparently as the result of evaporation of fluid in the superficial vessels. This increases the viscosity of blood and favors stasis. Cooling to -7° C. or heating to over 50° C. also leads to complete stasis. In the latter instance it is probable that evaporation also plays a contributing part, and in the former the crystallization of the water is of importance. Numerous chemical irritants may produce stasis, such as the corrosive alkalies and acids, hypertonic salt solutions, sugar, glycerin, croton oil and other substances. This may be due to chemical clotting of the blood or to precipitation of the blood proteins, or to the inflammation produced. Provided stasis be not too prolonged, circulation may be restored, but, if the process continue, clotting of the blood occurs and circulation is completely and permanently obstructed.

Local Anemia or Ischemia.—When, for any reason, the blood vessels of a part are constricted, there naturally follows a diminution of the blood content of the part, a local anemia or ischemia. Associated with this there is local blanching or pallor and, in certain areas, disturbances of sensation. Local anemia is commonly of nervous origin and is usually spasmodic in character. An example is seen in Raynaud's disease, in which there is symmetrical blanching of fingers or toes on both sides of the body, associated with tingling or pain and fall in local temperature. Somewhat similar, although apparently not of nervous origin, is the disease known as thrombo-angiitis obliterans. Ergotism also exhibits areas of local anemia. The local application of cold, of adrenalin, or of certain other drugs may also lead to local anemia. Reflex anemia of the skin surfaces may be produced by psychic disturbances such as anger and fear. Local or general anemia of the brain may be the direct cause of fainting, as the result of pain, fright, or other emotion. Reflex disturbances of this sort are likely to be only temporary and do not lead to serious secondary effects. Provided the constriction be of sufficient duration, the coincident reduction of nutrition may lead to a series of secondary changes such as cloudy swelling, fatty degeneration, atrophy, necrosis, or gangrene. Local interference with circulation may also be produced by obstruction to a supplying artery. This may result from pressure from without, from disease of the arterial wall, from thrombosis or embolism. Thrombosis signifies the formation of a clot in a living vessel. Embolism signifies the lodging in a vessel of some material foreign to normal circulation, including particles of thrombi, bacterial clumps, air, oil, and other foreign substances. For the sake of clarity, disturbances incident to obstruction of an artery will be discussed under the heading of infarction.

Infarction.—Infarction may be defined as the series of events following obstruction of the supplying vessel of a part, ultimately leading to necrosis.

It is frequently stated that the occlusion of an artery leads to anemia in its branches. While this is perfectly true functionally, in that the blood in those branches is no longer fit to supply nutrition and oxygen to the affected part, yet anatomically the vessels beyond the point of obstruction usually dilate so that the quantity of blood is increased. This simple statement, however, has been the subject of considerable controversy. Cohnheim, one of the first to study the problem was of the opinion that the condition in the branches of the obstructed artery, depends largely upon the anastomosis of the arterial terminals with those of other arteries. He formed the conclusion that if there be little or no anastomosis of arterial terminals, the obstructed area shows anemia, but if there be anastomosis the area may be hyperemic. The cause of the hyperemia in these areas has been variously interpreted. Cohnheim himself was of the opinion that backflow from the veins was important, but Mall showed that it is impossible to inject the arteries through the veins of the mesentery. Litten found that if he ligated all collateral sources of arterial blood supply, the hyperemia was less apparent than when these were intact, but that if the draining veins were ligated the hyperemia became more severe. Bier found that if, after section of the artery, the draining vein were also sectioned, dilated capillaries in the obstructed area remained dilated and filled with blood; and Brown-Sequard probably gave the correct interpretation when he pointed out that in all probability, along with the lesion of the supplying artery, there is also a disturbance of vasomotor nerves which determines dilatation. Our own studies of circulation are conclusive in demonstrating that the primary effect, following obstruction of an artery, is hyperemia in the area of distribution. Whether this hyperemia is followed by other more important changes depends largely upon collateral circulation, not necessarily that supplied by anastomosing arteries, but circulation established in any available way. For example, there is little anastomosis between the branches of the pulmonary arteries, but the anatomic structure of the lung is such that the capillaries come off directly from fairly large vessels. They may readily dilate so as to establish collateral circulation and to maintain nutrition. The maintenance of nutrition occurs even when the bronchial circulation is obstructed by ligature at its origin from the aorta. If, however, the collateral circulation be insufficient to maintain nutrition, the area involved undergoes deteriorative changes which finally result in necrosis. The infarct is the end result of the process of infarction. Complete occlusion of veins may occur without infarction, but occasionally, as in the kidney, the obstruction may result in death of the tissues or an infarct of venous origin.

Infarcts are often classified as anemic and hemorrhagic. This view has attained wide acceptance, due to its advocacy by Weigert, who opposed what we believe to be the correct view of Rokitsansky, namely, that the pale infarct represents a decolorization of an earlier hemorrhagic infarct. Forbes studied the question experimentally and came to the same conclusion as Rokitsansky, a conclusion which is supported by our own more extensive work. On the basis of these modern studies, it may be stated that infarction is a process which

probably throughout the body presents the same fundamental stages; and, depending upon the time when the infarct occurred and its situation, it may be either anemic or pale, hemorrhagic or red, or may show a mixture of these two. The simple observation of white infarcts and red infarcts in the same spleen, serves adequately to combat the view that these conditions differ because of differences in anatomical structure of the arteries. From experimental studies of infarction as seen in the kidney, spleen, heart and lung, it may be stated that changes occur in the following sequence. At first the area becomes hyperemic regardless of the general circulatory condition, except that differences in the amount of hyperemia may result from variations in general circulation. If all sources of collateral circulation be removed from an organ, the hyperemia is relatively slight, but in our experience it is not materially increased by damming back of blood in the venous circulation, except in the lung where infarction does not occur unless passive hyperemia is also present. Within two hours after the obstruction of the vessel, the blood corpuscles in the affected part begin to fuse together, and form conglutinated masses. The part becomes swollen as the result of hyperemia and of edema but the edema soon disappears. Cloudy swelling appears usually in about two hours and retrogressive changes progress until, at the end of forty-eight hours necrosis is present in the center of the infarct. The necrosis affects particularly the parenchymatous cells in the earlier stages but ultimately affects also the connective tissue elements. Hemorrhage is constant but varies in amount dependent upon the vascular supply of the organ. For example, hemorrhage in the spleen and the lung is much more marked than that in the kidney or in the heart. In these latter organs it may not be demonstrable grossly, but is always present upon microscopic examination. When necrosis appears, the margin of living tissue around the area shows a so-called reactive or collateral hyperemia, due in all probability to the irritant effect of the necrotic tissue. The necrotic area becomes anemic, or pallid, or white, because of decolorization following degeneration of the blood. The removal of the pigment is probably by plasmatic diffusion. The pigment is probably removed as hemoglobin because, with the exception of the spleen and the brain, pigmentation by granular or crystalline blood pigment is not common. The decolorization appears first in the center of the infarct and then progresses peripherally. Blood injected into the lungs experimentally is removed by endothelial cells and carried to the regional lymph nodes; and there is little doubt that this process serves to remove cells and granular pigment from the margins of the infarcts. Endothelial cells do not penetrate deeply into the infarct. The most important sequence of infarction is organization. This is a process whereby, as the result of a very low grade inflammation, connective tissue and capillaries grow so as to form a capsule around larger infarcts or to replace small infarcts completely. By gradual alteration of this tissue into adult type connective tissue, the infarct becomes either encapsulated or cicatrized. The details of this growth of connective tissue will be considered in the discussion of inflammation. When any area of tissue is destroyed there is, in some degree, regeneration of the destroyed tissues.

depending upon the type of tissue affected. Regeneration is discussed in the chapter on inflammation.

Hemorrhagic Infarcts.—Infarcts in general are the seat primarily of hemorrhage. The hemorrhage may not be visible grossly. It is customary to describe as hemorrhagic infarcts those in which the naked eye examination discloses a rich blood content. Such infarcts are seen in tissues where the blood supply is rich and the arrangement of the tissues rather loose. Consequently, the lung and the spleen show hemorrhagic infarcts to the best advantage. The infarct is generally conical in form, and occurs near the periphery of the organ with the apex toward the point of occlusion. The conical form may, however, be altered by the conformation of the outer surface of the organ. Affecting a margin of the spleen, the infarct may resemble a double cone or spindle. Affecting an oblique surface of the lung the form may be that of a truncated cone. Superficially the area involved is found to be swollen, solid, red, and firm. Not infrequently in the case of the lung, the pleural surface may be covered by a



FIG. 44.—Hemorrhagic infarct of lung.

thin film of fibrinous exudate. The color is dark red and any area of reactionary hyperemia in the margin can be differentiated by its brighter red color. The cut surface of such an infarct is generally triangular in outline, sharply defined, shows the same color as the outer surface, bulges above the surrounding tissue and, because of clotting of the blood with fibrin formation, usually is less moist than the surrounding tissue. The cut surface bleeds very little because of the fact that the blood is coagulated. Microscopically the infarct is usually well defined, and shows beneath the capsule or surface of the organ a narrow zone of tissue, uninvolved save for the marginal hyperemia. In the early stage hemorrhage is the most notable feature; the parenchymatous cells show cloudy swelling or even fatty degeneration. Later the parenchymatous and less resistant parts of the tissues show complete necrosis, whereas the connective tissue framework may be fairly well preserved. Ultimately, however, all tissues including the blood undergo necrosis. The necrotic areas show necrosis in the form of granularity or hyalinization of the cytoplasm, loss of cell outline, karyorrhexis, pyknosis or complete solution of the nuclei. In the earlier stages, the margins show the reactionary hyperemia in the form of distension of the blood vessels and, in addition, the exudation of a few polymorphonuclear leucocytes and infiltration of lymphocytes and endotheliocytes. Phagocytosis of cell fragments by the endotheliocytes is present but not striking. Accompanying these changes the marginal cells may show fat infiltration or fatty degeneration. Subsequently, this mild inflammatory reaction is followed by the growth of new blood vessels and connective tissue, constituting the process of organization spoken of above. Still later there is a dense margin of connective tissue around the infarct which may partially or completely replace the infarct.

White Infarcts.—Since the white, or “anemic” infarcts are pallid because of

decolorization of the blood in the original area of infarction, it follows that the less the hemorrhage the earlier does the infarct become pale. Hence those organs which do not have an extremely rich blood supply are more likely to show white infarcts than are others. Thus, of those organs where infarction is most frequent, white infarcts are commoner in the kidney and heart. Such infarcts however, are not uncommon in the spleen and are occasionally seen in the lung. In the earlier stages of the process white infarcts are swollen, but in the later stages, they show, as a rule, a certain amount of retraction of the outer surface. They are of the same shape as hemorrhagic infarcts; they are solid, are well defined and paler than the rest of the organ. The usual color of the pale infarcts is a light yellow. The cut surface is dry, granular and friable. Reactionary hyperemia about the margin is almost constant. Microscopically, the greater part of the area is found to be the seat of complete necrosis. If the original hemorrhage has been slight, all traces of blood corpuscles have disappeared. If the hemorrhage has been marked, there may remain, especially near the margins, the outlines of erythrocytes without hemoglobin, the so-called shadow cells. Toward the margin, red cells may be fairly well preserved and in general, necrosis is less marked at the margin than centrally. Reactive hyperemia is more apparent and organization further advanced than in the red infarcts. An infarct may progress to the white stage and may still show microscopically an outline of the connective tissue structure, but even though the outline remains, the connective tissue itself is usually completely necrotic. The necrotic cellular material of the organ substance is made up almost entirely of coarse granules, which take the acid stain. Infarcts of the spleen usually show blood pigment in the form of hematoidin, deposited in fine needle-like crystals collected together in sheaf-like bundles, the so-called "burrs." Hemosiderin is not commonly found in old infarcts except those of the brain, where it is collected in phagocytes at the margin.

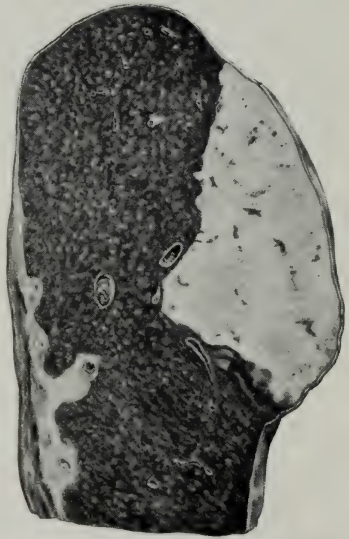


FIG. 45—White or "anemic" infarct of spleen.

There is usually present, over the base of the infarcts, a small line of living tissue which fails to become necrotic because of a more or less independent circulation, in and underneath the organ surfaces. In the case of the kidney and spleen this is provided by the capsular circulation. In the lung the pleural vessels course parallel to the surface of the pleura, and are not involved by the obstruction which produces the infarct. In the case of the heart the base of the infarct is toward the endocardium, where both endocardium and underlying cardiac tissue obtain their nutrition from the blood in the chambers of the heart and the Thebesian vessels. With the exception of the brain, infarcts

of which will be described in the section on neuropathology, other organs than those mentioned above are very rarely the seat of infarction. Such lesions are described in the liver, in the adrenal, in the pancreas, and are of particular importance in the intestinal canal. In this last situation the course of events does

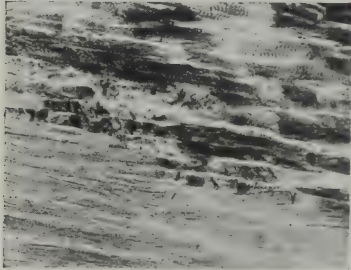


FIG. 46—Photomicrograph of experimental infarction of dog's heart, showing hyalin and granular necrosis of muscle.

not go on to white infarction, because during the hemorrhagic stage the necrosis of the gut wall leads to rupture, general peritonitis and death, unless the diagnosis be made and proper surgical operation performed.

Functional disturbances following infarction depend upon the size, number and area involved. In the brain, areas important for motor or sensory function or even structures necessary for life may be involved. In the lungs, the infarcts are usually relatively small and of little functional significance, although

at times the pleurisy over the surface may give pain and the sputum may be bloody. In the heart, small infarcts can be survived with little difficulty, but if the infarcts be sufficiently large the wall may be weakened and local dilatation ensue. Subsequently, this may rupture because of the intracardiac pressure. Sudden death may follow embolic occlusion of a sufficiently large part of the coronary circulation. The amount of circulation which must be obliterated to produce death, depends to a certain degree, upon the condition of the heart muscle. Large infarcts of the spleen may produce pain for a short time, but otherwise are of no functional significance. Infarcts of the kidney may produce pain and rarely lead to hematuria, but in the absence of other disease of the kidney, infarcts must be multiple and large to produce any clinical manifestation. If the tissue destruction be sufficiently extensive, there may be fever, due presumably to the absorption of protein split products.

The retrogressive changes in the dead cells depend upon autolysis, a process that has been discussed in connection with the subject of necrosis. The fact that in infarcts of the spleen, and of certain other organs, the connective tissue nuclei and the nuclei of the lymphocytes fail to disappear until relatively late, has led to the suspicion that there may be an enzyme which operates especially upon cytoplasm.

The removal of the necrotic material depends in part upon the activity of the phagocytic cells, but anatomical study of infarction shows a relatively small participation on the part of these cells. Corper found that during the earlier stage of infarction when the nuclei show relatively little change, there is practically no solution of protein or protein products. Even when nuclei can no

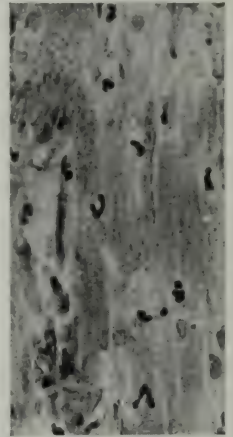


FIG. 47—Photomicrograph of experimental infarction of dog's heart, showing migration of a few leucocytes into the necrotic muscle.

longer be found, from 30 to 50 per cent. of the protein material is still in the insoluble form. This is in harmony with the customary slow reduction in the size of infarcts. In our own experimental observation the infarcts were only slightly reduced in size at the end of six weeks. In man, infarcts in various organs are observed which are only slightly reduced in size, while the causative disease of heart valves is completely cicatrized, thus indicating that the infarcts are very old. Wells points out that the inhibition of autolysis is probably due to the seeping of the alkaline tissue fluid through the infarcted area. Our own studies would indicate that phagocytosis plays only a small part in the removal of the necrotic material and that the materials which are rendered soluble by the lytic processes are removed by plasmatic diffusion. Endotheliocytes and perhaps other cells at the margins of infarcts not uncommonly contain fat. It is not limited to infarcts, however, and may be seen about any area of necrosis. The destruction of tissue is accompanied by breaking of fat into glycerol and fatty acids. These diffuse to the margin of the infarct where remaining cell lipase synthesizes fat.

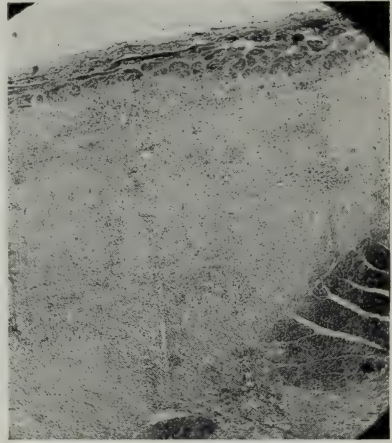


FIG. 48—Low power photomicrograph of experimental infarction of dog's heart in stage of complete cicatrization. Note pyramidal outline and the preservation of muscle under the endocardium.

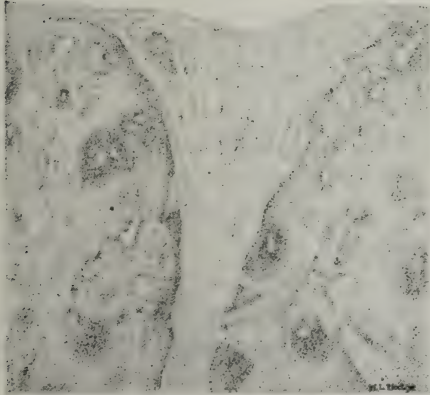


FIG. 49—Low power drawing of old scar of infarct in human spleen.

Thrombosis. Mechanism of Clotting.—Blood is maintained in the fluid state by virtue of a delicate balance of its constituents, a balance which may be upset by alterations of these constituents and by alterations of the environment of the blood. This upset of balance results in clotting. The clot is produced by the formation of fibrin, which represents what is practically an irreversible colloidal precipitate. With minor reservations, the mechanism of fibrin formation as proposed by Howell is generally accepted. Prothrombin and antithrombin are present normally in the circulating blood in a state of balance. When blood

is shed, its constituent formed elements deteriorate and the plasma undergoes important changes. From the platelets and tissues is liberated a thromboplastin which neutralizes the antithrombin and releases the prothrombin. This is activated by the calcium of the blood, thrombin is formed and acts upon fibrinogen to produce fibrin. Morawitz considers that the formation of thrombin depends upon the interaction of prothrombin or thrombogen originating

in the platelets, thrombokinas which originates from the leucocytes and calcium in solution in the plasma. Bordet and Delange explain the formation of thrombin as due to the interaction, in the presence of calcium salts, of cytozyme derived from the platelets or tissue cells, and serozyme which exists in the plasma. The nature and mechanism of clotting are still the subject of study. Antithrombin according to Howell is formed by the action of a phosphatid from the liver upon a pro-antithrombin. Prothrombin exists in the plasma and is derived from platelets and leucocytes. That it is identical with the material

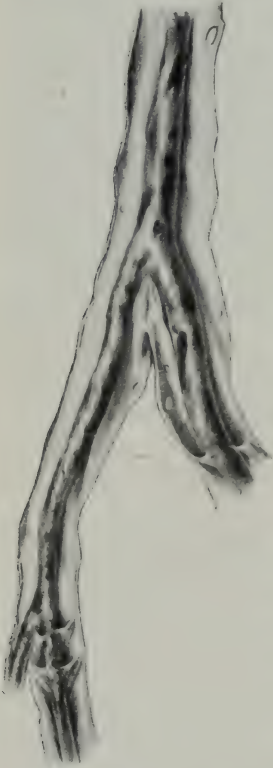


FIG. 50—Extensive thrombosis of a vein and its tributaries. The vein has been laid open and shows the valves.

acting similarly and derived from the tissues is not certain, but the action appears to be essentially the same in both cases. Microscopic examination of clots shows what appear to be centra of degenerated platelets and leucocytes, but this cannot necessarily be interpreted as meaning that these cells must deteriorate to produce prothrombin. Thrombin is a soluble substance that may be extracted from protein precipitates of blood, and is destroyed by heating to 60° C.; otherwise its constitution is unknown. Originally it was believed to be an enzyme but no proof has been advanced to support this view. It is formed in excess in the clotting of blood and can be demonstrated in the serum. Fibrinogen is a simple protein related to the globulins and, according to Matthews, in its natural condition is closely associated with a phospholipin of some kind. Goodpasture ascribes its origin to the liver and intestine, an opinion concurred in by Whipple. Fibrin is a refractile protein substance deposited, according to Matthews, as fluid crystals which fuse to form the network which enmeshes the corpuscles of the blood to form the clot.

The physical conditions, which maintain the blood in fluid condition in the vessels, are dependent essentially upon the integrity of the lining of the vessel. While it is true that ligatures may be placed around blood vessels and the blood remain fluid for a considerable time, yet ultimately this blood clots. There is no evidence that there is an anticoagulative substance in the endothelium, nor that there is sufficient material of fatty nature to oil the lining cells of the vessels. The rate of circulation of the blood through these vessels also is of some importance in maintaining the fluid state of the blood, as is indicated by the experiment just quoted. Slowing of circulation, however, is only likely to be associated with clotting where there are irregularities in the lining wall, as for example near the pectinate muscles in the cardiac atria, or as the result of diseases of the vascular wall.

Numerous conditions may accelerate or retard clotting of the blood and produce variations in the consistency of the clot. Increases in the amount of

fibrinogen, in the number of platelets and of leucocytes may favor clotting. Similarly decreases of important substances such as fibrinogen, blood platelets and other elements may lead to retardation of clotting. Inasmuch as clotting is one of the conditions which limit hemorrhage, inhibition of clotting is important in the hemorrhagic diseases. Contact with the tissues and with foreign bodies favors clotting, and the injection of properly prepared tissue extract may produce clotting in the living animal. A wide variety of substances may retard or prevent clotting, such as the extract of leeches (which in pure form is called *hirudin*), heparin, oxalates, fluorides and citrates, as well as strong solutions of magnesium sulphate and sodium chloride. Oxalates or fluorides combine with calcium so as to prevent its action in clotting. Citrates probably maintain calcium in an un-ionized form and similarly prevent clotting.

Forms of Clot.—When blood is clotted the fluid constituents are altered in character, and are in a general way not further coagulable by the interaction of fibrinogen and thrombin. There can be distinguished from the solid clot this altered fluid which is called serum, and is to be differentiated sharply from the normal fluid of the blood which is called plasma. When blood is shed externally or into containers of some sort, which are not specially treated, the clot forms a jelly-like red mass from which the colorless or pale yellow serum separates. If citrate or some of the other salts mentioned above be added, or the blood be taken into paraffined vessels, clotting may be retarded and it is possible to obtain plasma from this material. The blood may also be maintained in a fluid state by whipping out the fibrin with foreign bodies, such as glass rods, or by glass beads shaken up in the freshly shed blood. Here, however, the blood is materially altered and the fluid mixture is made up of serum and corpuscles, the so-called defibrinated blood.

Of considerable importance in pathological diagnosis is the postmortem appearance of blood clots in the vessels after death. Usually the blood in the vessels clots rather suddenly after death, and in the clots are enmeshed all the elements of the blood, producing a red clot similar to that seen outside the body. This is called the “currant-jelly” clot. But infrequently, where death occurs rather slowly, the elements of the blood may separate out to a considerable degree by virtue of differences in specific gravity, so that portions of the clot which lie in a superior position in the body may be of rather brilliant yellow color, and are called “chicken fat” clots. Sometimes also in the neighborhood of the chordæ tendineæ of the atrioventricular valves, the whipping action of these cords may separate the fibrin to produce a white fibrin clot, enmeshing very few cells. The “currant-jelly” clot, therefore contains all the cellular blood elements; the “chicken fat” clot contains principally white blood corpuscles, and the white fibrin clot has little or no corpuscular content. The presence of fibrin differentiates clots from simple clumping together of corpuscles. The fibrin serves to bind together the elements of the clot and give it a certain degree of firmness. If present in large quantities it gives a gray color to the clot and in cut surfaces a dry appearance. Microscopically fibrin appears in the form of fine, refractile, acid staining fibrils varying somewhat in size, branching

and anastomosing to form an irregular mesh, which may resemble somewhat the fibrils of connective tissue. The fibrin mesh represents a precipitate from the fluid of the blood, and at the lines of junction there is an increase in amount of material which produces the so-called fibrin nodes. Not infrequently, certain small centers of platelets or leucocytes appear from which the lines of fibrin radiate to form the so-called fibrin asters or stars. Under certain conditions blood in small vessels, may, by virtue of stasis, undergo conglutination or congelation, in which the corpuscles fuse together in a relatively solid mass without any fibrin formation. Numerous substances, including specific aggluti-



FIG. 51—Thrombosis in an auricular appendage, the so-called marantic thrombus. The irregular spaces of the appendage appear as lakes in the heart muscle and are filled with a clot rich in fibrin.

nating sera, as well as a wide variety of colloids, may produce agglutination in the circulating blood and these agglutinated masses may lodge in small vessels to occlude them.

Thrombosis.—Thrombosis signifies clotting of blood in living vessels. The important conditions which predispose to thrombosis in the vessels include injury to the vessel wall, alteration of the constitution of the blood, slowing of the stream and eddies in the current. Alteration in the vessel wall which leads to roughening may be produced by chronic conditions such as arteriosclerosis or aneurysm, and more particularly infectious processes leading to endothelial degeneration, or partial destruction of the wall; mechanical injury to the

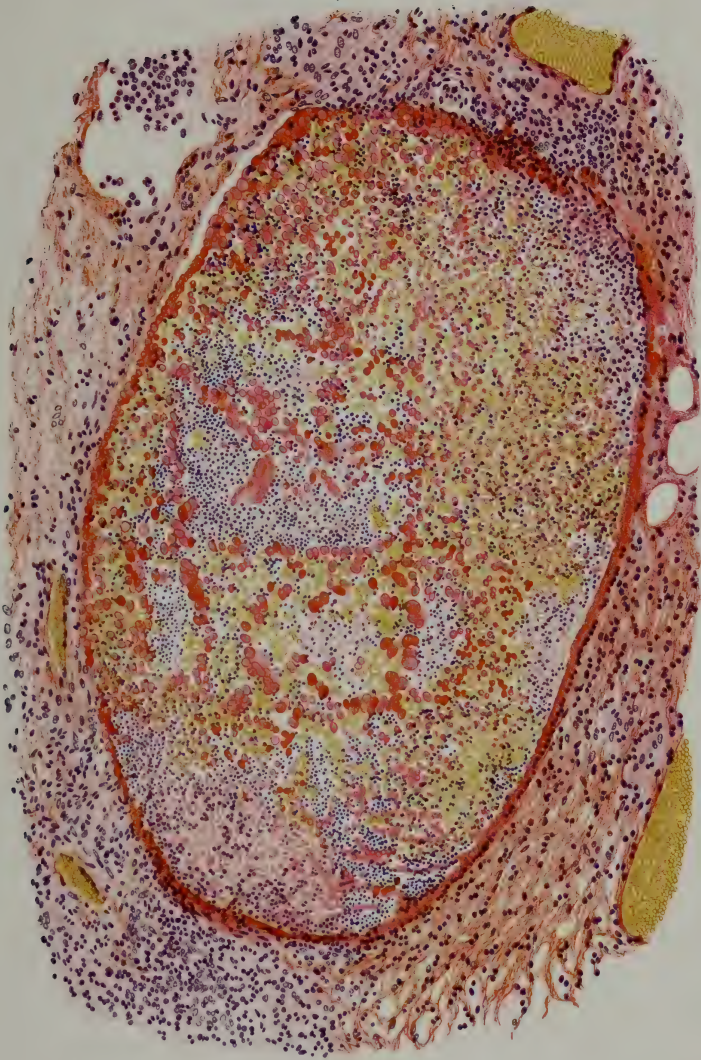


PLATE V—Early thrombosis of a vein, showing red and white corpuscles, agglutinated platelets and a small amount of fibrin.

vessel wall may also lead to thrombosis. It is perfectly true, however, that injury of the vessel wall may be produced without leading to thrombosis of any moment, as for example, in careful suturing of the vessel wall. Many pathologists maintain, that in order for injury of the vessel wall to lead to thrombosis, there must also be slowing of the current. This slowing of the current may be of very moderate degree, since thrombosis on the roughened wall of the aorta the seat of arteriosclerosis, where slowing cannot be very marked, is not uncommonly observed. The influence of slowing of the current is seen in the fact that thrombosis is distinctly more common in veins than in arteries, and especially in those veins where under certain circumstances the current is likely to be especially slow. Similarly, the fact that thrombosis occurs in aneurysm and in dilatations of the veins is probably due in large part to the slowing of, or production of eddies in, the current. General passive hyperemia also produces a tendency toward thrombosis, probably because of increased viscosity due to accumulation of carbon dioxide. When the stagnation of the current goes on to cessation, as is seen following ligation of a vessel, thrombosis in some degree almost invariably appears. Although careful ligation of vessels may produce thrombosis simply at the site of ligation, yet, as a general rule, thrombosis appears in the entire column of blood which is interrupted. Therefore, it extends to the next branch above and the next branch below. In addition to the slowing of the current and alterations of the vessel walls, any of the factors described above as favoring clotting also operate to favor thrombosis. The term hyperinosis is sometimes used to indicate an altered state of the blood favoring clotting, whereas hypinosis indicates a condition which inhibits clotting. There is little doubt that, in addition to the factors mentioned, increased viscosity of the blood favors thrombosis. Little information is available as to certain vague changes in chemical composition or physical states which are said to favor thrombosis.

Relation of Bacterial Infection to Thrombosis.—Bacterial infection is of the utmost importance in thrombus formation, and may operate through any of the three methods outlined above. Bacteria may produce roughening of vascular walls, they may produce slowing of the current or they may produce alteration in the constitution of the blood. To lead to any or all of these alterations, bacteria may be present in foci in the body or may actually invade the blood stream. In the first instance damage is due to products of the bacteria which are absorbed. In the second instance the damage is due to both the bacterial bodies and to their products. The presence of bacteria in the body may lead to local inflammatory reaction, which in the case of the pyogenic bacteria and certain other organisms, results in the formation of abscesses or other types of suppuration. As the bacteria proliferate and the inflammatory process extends, the latter comes in contact with blood vessels. In thin walled vessels thrombosis may ensue without direct involvement of the vessels by the lesions. This is believed to be due to diffusion of bacterial products, which so injure the endothelial lining of these vessels as to produce roughening and thrombosis. When the inflammatory processes involve the vessel walls the

same phenomenon occurs, and when by extension they penetrate through the wall, thrombosis is the natural reaction. Bacteria in the blood stream may lead to thrombosis either by breaking off fragments of an infectious primary thrombus, with subsequent lodgment in other vessels, or by the actual deposit of bacteria or clumps of bacteria in vessels. In either case, inflammation is set up and thrombosis occurs. The presence of bacterial infection in the body may alter the constitution of the blood in two ways. In intense infection, it is not

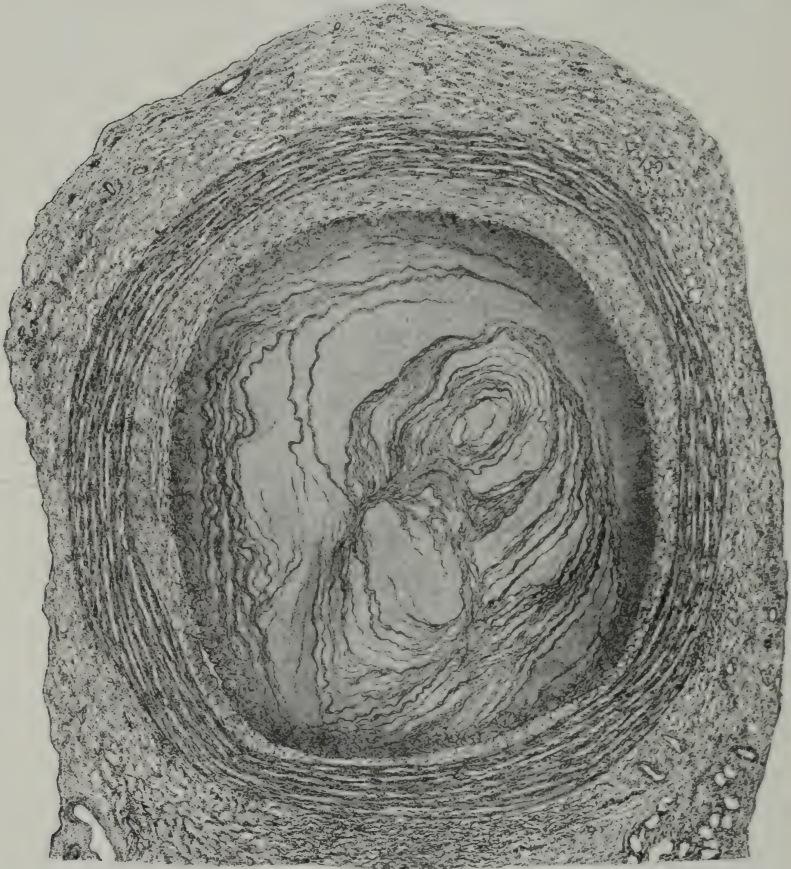


FIG. 52—Thrombosis in a vein. The fibrin masses are irregularly distributed. Magnification is too low to show cells clearly.

uncommon to find clotting retarded so that multiple hemorrhages may occur, particularly under the skin and serous surfaces. On the other hand, bacterial infection may so alter the blood constitution as to favor thrombosis. These changes are probably due to products of the bacteria rather than the bacterial bodies themselves, but exactly what constituent of the blood is affected, is not precisely known. As has been pointed out in discussing degenerations, bacterial products may produce parenchymatous degeneration of heart muscle and of vascular muscle, so as to reduce blood pressure and lead to slowing of the current, which of course favors thrombosis. In a study of thrombosis in

man, Lubarsch was able to exclude an infectious agent in only 13 per cent. of the cases.

Construction of Thrombi.—Depending upon construction it is possible to differentiate mixed thrombi, red thrombi and hyaline thrombi. The most common and most important are the *mixed thrombi*. Grossly, these are found adherent to the vessel walls, and in this way can be distinguished from post-mortem clots. The thrombus is firm and on cross section shows a mottled mixture of gray, yellow and red. Microscopically, it has a rather complicated architecture which shows an irregular network of fibrin, masses of blood platelets more or less fused together, masses of leucocytes, masses of red blood corpuscles and areas in which these cells are mixed together. Aschoff has shown that such thrombi originate primarily by a deposit of platelets at the site of lesion of the vessel wall. Secondly, there is a deposit of fibrin and further accumulation of platelets which form a tree-like or coral-form support, or scaffolding, for the deposit of the other cells. As the primary thrombus is laid down, this leads to alteration and whorling of the circulating blood in the neighborhood, so that under different circumstances the deposit of cells may be white blood corpuscles, or red blood corpuscles or mixtures of the two. It is of importance to differentiate between the gross appearance of postmortem clots and antemortem thrombi. The postmortem clots are usually of the type called “currant jelly.” They are of jelly-like consistence, elastic, moist and of homogeneous character, not attached to the vessel wall, easily removed and may upon removal appear as a branching cast of the vascular tree. The antemortem thrombi are usually firm, friable, dry, laminated or mottled in character, sometimes with a softened center; they are more or less firmly attached to the vessel wall and when removed may leave a somewhat roughened vessel wall. Both postmortem clots and antemortem thrombi may be present in the same vessel, but if so they are usually well delimited one from the other and readily distinguishable.

Red thrombi are those which are made up of the blood constituents in about normal proportions. When a vessel is ligated the sudden stoppage of blood in that vessel leads to the formation of a red thrombus. At first this is not adherent to the vessel wall, but soon becomes so owing to degenerative changes in the vessel wall, and to the process of organization which will be discussed later. The same thing occurs when a vessel becomes completely occluded by thrombosis, or is blocked by means of an embolus or tumor growth. If the blood current be extremely slow, due to other disease, the presence of a small white or mottled thrombus in the vessel wall may lead to the development of an occluding red thrombus, probably because of a disturbance of relation of blood constituents in that particular area. If, however, the circulation be fairly rapid, this type of thrombus is not likely to occur secondary to anything other than complete occlusion. Microscopically, such a thrombus is found to be made up of a loose network of fibrin enmeshing many red blood corpuscles, a few leucocytes and a moderate number of platelets.

White thrombi are made up almost entirely of platelets, and are deposited

as a rule because of a lesion of a vessel wall, apparently regardless of whether the circulation be slowed or normal. They can be produced experimentally by injuring the vessel wall by a corrosive such as silver nitrate solution, which when painted on the outside of a vein leads to the development of thrombi within. In man, such thrombi may be seen on the roughened aortic wall of arteriosclerosis. As a rule, however, there is a small admixture of fibrin and leucocytes. It is supposed that the normal smoothness of vessel walls permits the free passage of such sticky cells as the leucocytes and the platelets, but when the continuity of the lining is interrupted, these no longer flow with normal freedom,

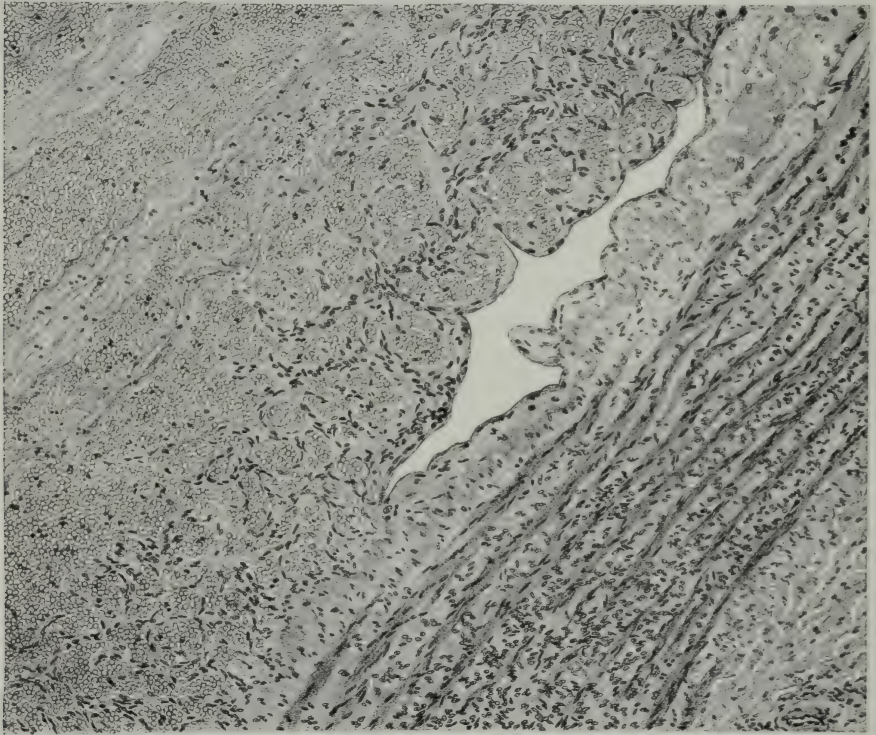


Fig. 53—Early organization of a thrombus in a vein. The young connective tissue cells are found within that part of the thrombus near the wall of the vein.

adhere to the roughened surface and produce thrombi. These thrombi are not infrequently the primary change in that disease of the heart called acute endocarditis, where they develop quite independently of slowing of the circulation. In those instances where the leucocytes predominate, the thrombus has a pale yellow appearance and is referred to as a *leucocyte thrombus*. The *fibrin thrombi* mentioned in connection with postmortem clotting of blood rarely appear during life, but apparently are thrown down rather in the agonal period. *Hyaline thrombi* occur particularly in smaller vessels such as the capillary loops of the renal glomerulus, the capillaries of the lungs, the sinusoids of the liver. They are not visible grossly, but microscopically are found to be made up of masses occluding these vessels and exhibiting simply a hyaline acidophilic

character. It is probable that they may originate in small masses of fibrin which occlude the vessels, or small agglomerations of red blood corpuscles which plug the capillaries. In either case subsequent changes lead to the formation of hyaline substance. Hyaline thrombi occur in infectious diseases such as diphtheria, scarlatina, pneumonia and peritonitis. They may also be produced by poisoning such as that of snake venom, poisonous fungi, certain ferments, extensive burns, eclampsia, and may be produced experimentally by the injection of certain poisons such as uranyl nitrate. They may be produced experimentally also by the injection of an agglutinating serum, which leads to the lodgment of small clumps of cells in vessels and subsequent hyaline transformation. Hyaline thrombi may occur in blood transfusion in man as the result of the injection of incompatible blood which produces agglutination of the donor's corpuscles.

Types of Thrombi.—Certain terms are applied to thrombi depending upon their form and situation. The so-called autochthonous thrombi are those which are laid down upon the wall of a vessel as a sequence of alteration in the lining of the vessel. These may be either simple mural thrombi, or they may have a point of attachment with a pedicle so as to constitute valve-like thrombi. Occluding or obstructive thrombi are those which obliterate the lumen of the vessel. From these may develop secondary thrombi which extend in a progressive manner either up or down the vessel. This type of progressive thrombus must be differentiated from the obscure disease known as progressive thrombosis, in which thrombi appear, either as the result of injury or spontaneously in the veins of an extremity, subsequently involve the veins of other extremities, and may become fairly widely generalized. A thrombus originating a short distance below a branch in a vessel, may extend up that vessel to the branching point, and then down the other branch so as to form a Y-shaped clot, the so-called saddle thrombus. In the heart, thrombi may be situated upon the walls of the ventricle to form mural thrombi, upon the valves to form vegetations, or may lie in the cavities so as to produce globoid thrombi; if these be attached to the heart wall by a pedicle, they constitute the so-called ball valve thrombi. The marantic thrombus is one which occurs where the circulation is slowed and is seen most commonly in the auricular appendages, more especially in those who die after atrial fibrillation. Here the circulation is slowed and the pectinate muscles produce irregularity of internal surface, so that mottled thrombi or red thrombi are frequently found.

Sequels of Thrombosis.—Aside from interrupted or altered circulation produced by thrombosis, there are certain changes which occur in the thrombus itself. The clotting of blood, whether within the vessels or outside the vessels, signifies the death of that fluid tissue. Leucocytes are embedded in practically all thrombi and when death occurs are likely to liberate autolytic ferments. These lead to softening of the clot. The softened mass is usually grayish-red in color and of semifluid or granular character. Lysis may extend to the surface of the clot and liberate fragments into the blood stream. This bland or asepticsoftening is to be distinguished from septic softening due to the presence

of, or invasion by, bacteria. Bacteria may be present at the time of the thrombosis, they may invade from surrounding suppurative lesions, or may be conveyed to the thrombus by the blood stream. The softening of a bland thrombus leads in most cases simply to the presence of small infarcts in other tissues, or if the emboli lodge at vital points, serious symptoms or death may follow. The softening of an infected thrombus discharges infected emboli, which lodge in small vessels and lead to the development of multiple abscesses in various parts of the body, a condition called pyemia. Not only may infected thrombi produce pyemia, but they may serve as a point of bacterial growth from which poisonous substances enter the blood to produce toxemia, or bacteria may be discharged into the blood stream to produce septicemia. The infected thrombus

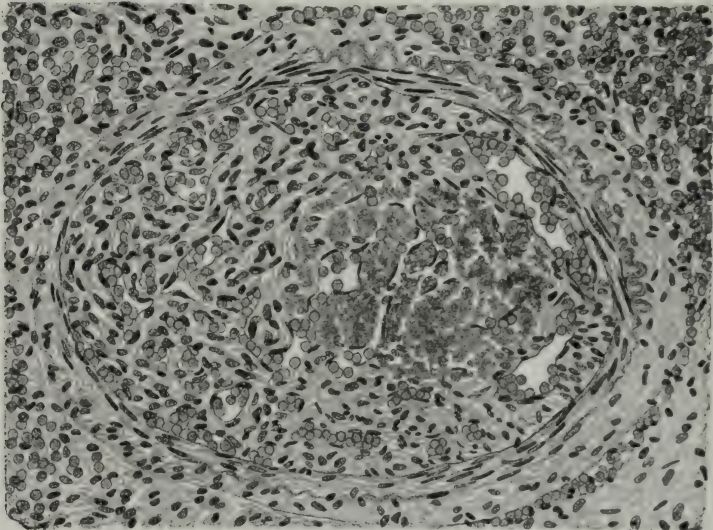


FIG. 54—Almost complete organization of a thrombus in a small branch of the pulmonary artery. The new connective tissue cells are accompanied by minute capillaries.

itself is a focus of suppuration, which may invade and extend through the vessel wall so as to produce hemorrhage or infect surrounding tissues.

Organization and Canalization.—A thrombus in a vessel is made up of dead blood and, as is the case with dead tissue elsewhere, serves as a foreign body to excite a low grade of inflammation. As the fluid part of the clot is removed by absorption, the contraction of the clot brings to bear a certain amount of tension on the vessel wall. These factors operate as a stimulus to connective tissue growth, which proceeds from the vessel wall into the thrombus and, in order to provide nourishment, small capillaries accompany the connective tissue cells. This leads ultimately to practically complete substitution of the thrombus by a connective tissue and capillary mass. The connective tissue subsequently becomes of adult type, the small blood vessels disappear and the thrombus is said to have become organized. While this is going on the end surfaces of the thrombi become covered with endothelial cells, which grow from

the endothelial lining of the vessel. As a part of the organization, canalization sometimes occurs. The canals in the thrombus probably develop from the small capillaries which accompany the connective tissue growth. These capillaries constitute an intricate network throughout the thrombus. As they appear near the end surfaces of the thrombi, they may break through to the lumen of the vessel. If this occur on the end upon which the impact of circulation is felt, the pressure of the circulation may dilate these vessels and establish irregular lines of communication through the clot. By further dilatation of the communicating vessels, circulation may be to all practical intents completely restored. In large vessels a certain amount of the canalization may be participated in by the vasa vasorum. In certain situations, notably the spleen, thrombi may undergo calcification to form the so-called phleboliths.

Other Forms of Thrombosis.—In addition to the forms of thrombi mentioned above, attention may be called to certain other forms which occur. Not only do the acute infections lead to thrombosis but the more chronic infections may do likewise. Tuberculosis in its development may directly invade vessel walls and induce thrombus formation, or in cases where the bacilli float in the blood stream they may lodge and produce tubercles of the intima. Syphilis may lead to thrombosis because of syphilitic inflammation of the vessel walls, or its special lesion, the gumma, may extend directly into a vessel wall and induce thrombosis. Of great importance is the invasion of blood vessels by malignant tumors. The malignant

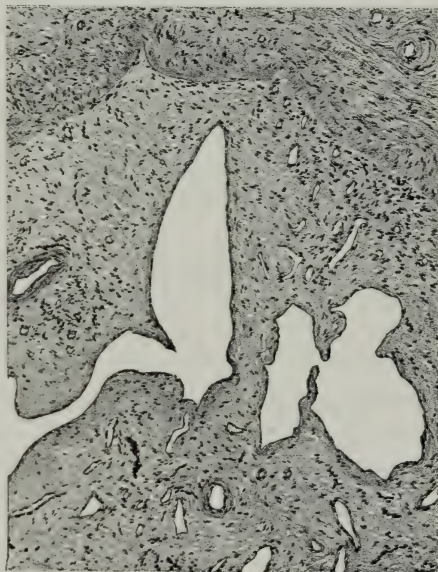


FIG. 55—Canalization of a thrombus. A section of an old thrombus of the jugular vein. The connective tissue is dense and poor in nuclei. The canals are variable in size and outline.

connective tissue tumors or sarcomas are the common offenders, but the malignant epithelial tumors or carcinomas may also act in this way. This invasion leads to tumor formation in the vessel, spoken of as tumor thrombus. Such a thrombus may grow along the walls of vessels and become very extensive. When the tumor growth does not occlude the vessel, secondary red or mottled blood thrombi are likely to appear and produce obstruction. Numerous instances of widespread extension of sarcoma are on record, but the commonest instance is the spread of the hypernephroma, a tumor of the kidney, through the renal vein into the cava. Such extensions of carcinomas are not so common.

Thrombi in the lymphatic vessels are commonly made up of tumor masses. Neighboring acute inflammation may bring into the lymphatics sufficient plasma and leucocytes to produce lymphatic thrombi.

Embolism is defined by Welch as "the impaction in some part of the vascular system, of any undissolved material brought there by the blood current. The transported material is an embolus. Embolism may likewise occur in lymphatic vessels." Emboli may be solid, liquid or gaseous.

Solid Emboli.—The term embolus usually indicates that the material is a fragment of a thrombus. As has been indicated above, thrombi readily undergo softening, and may easily be broken down so as to liberate fragments in the blood stream. The most frequent origin of this type of emboli is the thrombosis on heart valves in acute endocarditis. Other sorts of solid emboli include fragments of tissues such as small pieces of heart valves, tumor cells, parenchymatous cells, vegetable parasites, particularly bacteria, animal parasites such as the cysticercus of tenia echinococcus, small masses of calcified material, pigment granules and foreign bodies. From the point of origin, the emboli are carried by the blood current until they reach a projecting point in a vessel or more usually until they reach a vessel whose lumen is too small to permit passage of the material. Thus an embolus originating in a thrombus of mesenteric veins, may be carried through the inferior cava to the right heart and thence to the lungs. Similarly an embolus originating in an acute endocarditis, may be carried to practically any part of the arterial circulation. Welch states that the order of frequency of lodgment of emboli is approximately as follows: pulmonary, renal, splenic, cerebral, iliac and lower extremities, axillary and upper extremities, celiac axis with its hepatic and gastric branches, central artery of the retina, superior mesenteric, inferior mesenteric, abdominal aorta, coronary arteries of the heart. He points out, however, that judgment is somewhat difficult owing to the fact that minute emboli may lodge in small vessels of the extremities, or in the hepatic artery or other situations, with no apparent damage and no reason for suspecting their presence. Very rarely emboli may be so large as to obstruct the orifices of the heart. Aberrant embolism includes unusual forms, such as paradoxical embolism and retrograde embolism. *Paradoxical or crossed embolism* indicates that an embolus originating in a vein lodges in the arterial circulation, from which it normally is separated by the capillaries of the lung. The pulmonary capillaries are somewhat larger than the systemic capillaries and subject to a certain amount of dilatation, so that it is possible that solid particles may pass through the lungs and lodge subsequently in the systemic circulation, but is not probable that this will give rise to embolism of any considerable size. In most of the cases of paradoxical embolism it has been possible to demonstrate a patent foramen ovale and indeed, emboli have been found lodged there. It is generally assumed, therefore, that paradoxical embolism is the result of passage of emboli from the right to the left side of the heart through this opening. Emboli of tumor cells may pass through the pulmonary circulation, lodge in capillaries in the systemic circulation, and cause widespread secondary new growths. Bacterial emboli may be similarly distributed. *Retrograde embolism* occurs in the venous circulation when an embolus lodges in a vessel whose branch, or whose point of origin, is further from the

heart than the point of origin of the embolus. It is possible that there may be a backflow of blood from the heart following a period of positive pressure in the thorax such as is caused by coughing or forced respiration. Ribbert is of the opinion that the backward flow is due to marked stagnation of blood in the veins, permitting of a slow backward pressure of the solid particles in the vein. It may safely be stated, however, that at the present time no completely satisfactory explanation for this phenomenon can be offered. The *saddle* or *riding embolus*, is one which lodges at the bifurcation of a vessel and remains there with smaller divisions extending down into the branches.

Cells may be broken loose and float as emboli. Liver cells may appear in the pulmonary capillaries as the result of liver necrosis. Bone marrow cells may be found lodged in liver and lung capillaries as the result of infectious disease, leucemia, anemia, surface burns, or without demonstrable cause. Cells of the chorion may gain access to the circulation during or following normal pregnancy, or as a sequence of chorionepithelioma. Mallory maintains that the liver necroses of typhoid fever are due to endothelial cell emboli from the spleen and lymph nodes. With this exception, and with the exception of secondary tumor nodules arising from embolic tumor cells, cellular embolism is of little significance.

Sequences of Solid Emboli.—When emboli lodge they produce conditions favorable to the formation of thrombi, so that secondary thrombosis is practically always present. If the embolus completely occlude the vessel, the thrombus is usually a red thrombus, extending to the next branch of this vessel. If it simply lodge in the side of a vessel owing to a projection from the wall, it may lead to the formation of a mural thrombus, which increases in size until occlusion results. If the vessel be examined shortly after the lodging of the embolus, it is easily possible to distinguish between the embolus and the secondary thrombus, but if considerable time has elapsed, this distinction may not be possible. The identification of the embolus rests on its similarity to the thrombus or tissue from which it originated. As has been pointed out in the discussion of infarction, if collateral circulation be sufficient, the only interference in circulation beyond the lodgment of the embolus, is a dilatation of vessels and hyperemia. If, on the other hand, collateral circulation be not sufficient to maintain nutrition, infarction occurs. If pathogenic bacteria be present in an embolus, the secondary changes include those incident to the presence of bacteria, ordinarily suppuration. If the embolus be such a body as the scolex of the tenia echinococcus, it may increase in size so as to produce an echinococcus cyst. Tissue cells and fragments produce effects not differing from those produced by the ordinary type of embolus, and the same is true of the lodgment of pigment granules, masses of calcareous material and of foreign bodies. In the Great War, the transport of fragments of projectiles sometimes occurred and even in civil life the transport of foreign bodies, such as a fragment of needle introduced through the skin, sometimes occurs. The lodging of tumor cells leads usually to the development of secondary tumors or metastases.

Embolism in the lymphatic circulation is difficult to demonstrate except in the case of embolism of tumor cells. Under these circumstances the tumor grows and invades the lymphatic vessel, and certain small cells or groups of cells are broken off and carried in the lymphatic current. These usually find lodgment in the neighboring lymph nodes. After growth of the tumor in the lymph nodes, the latter may become so obstructed as to establish a retrograde lymphatic flow, under which circumstances retrograde transport of tumor cells may occur. This is discussed more fully in the chapter on tumors. Other conditions may also obliterate the lymphatic flow in lymph nodes, and establish retrograde flow, such as tuberculosis. Thus bacteria may be carried from the site of infection to the lymph nodes, excite disease there and then be carried in other directions by retrograde flow. This applies not only to tuberculosis but to the more acute infections such as those produced by the pyogenic bacteria.

Fat Embolism.—The transport of fat in the circulating blood in globules sufficiently large to produce obstruction in capillaries or small arteries is not uncommon. Welch regards fat embolism as next in sequence to embolism from broken down thrombi. It now seems probable that in the majority of cases, fat embolism is of little or no clinical significance. It occurs in man as the result of trauma, such as fractures of bone, injury to bones without fracture, and in operations upon obese subjects as discussed by Bissell. Gauss states that cases of fat embolism supposedly due to osteomyelitis have not been authenticated. Fractures are usually of greater significance when several bones are involved than when only one is broken. With any of these causes, it must be assumed that veins are injured so that the globules of fat directly enter into the blood current. The globules are then transported into the pulmonary circulation, where they appear as globules and cylinders in the smaller vessels and capillaries. At times the amount of fat may be so great as to obstruct vessels of considerable size. Smaller globules may pass through the pulmonary capillaries and enter the arterial circulation, whence they may lodge in the glomeruli of the kidney, in the small vessels of the brain, in the small vessels of the heart and in other situations. The clinical symptoms include rapid respiration, prostration, fall of blood pressure, pulmonary edema, and a small, rapid pulse. Symptoms referable to cerebral involvement may be seen occasionally in vomiting, convulsions, and coma. The symptoms appear from twelve to twenty-four hours, more or less, after the injury or operation, and resemble very closely surgical shock. Porter was of the opinion that fat embolism is the cause of traumatic shock but this has been contradicted by Warthin, Wiggers, Simonds and others. The physiology of surgical shock with its vascular dilatation and passage of fluid from the vessels into the tissues, is certainly different from that of fat embolism. Wiggers found that following injection of oil in the dog, there might be no apparent affect, there might be a rise in arterial pressure followed by restoration, or there might be a marked drop in arterial pressure followed by death in a few minutes. Electrocardiograms show that the heart in fatal cases does not fibrillate and that the mechanism is normal throughout.

He considers that death is due to respiratory failure brought about by fat embolism in the medulla. Simonds found that coincident with the fall in arterial pressure, there is a marked rise in venous pressure. Wiggers similarly found that the pressure in the right atrium is considerably increased, apparently due to cardiac failure from asphyxia. These changes in circulation can be explained as due to obstruction in the pulmonary circulation. Fat embolism should be suspected in any cases of sudden death following the injuries

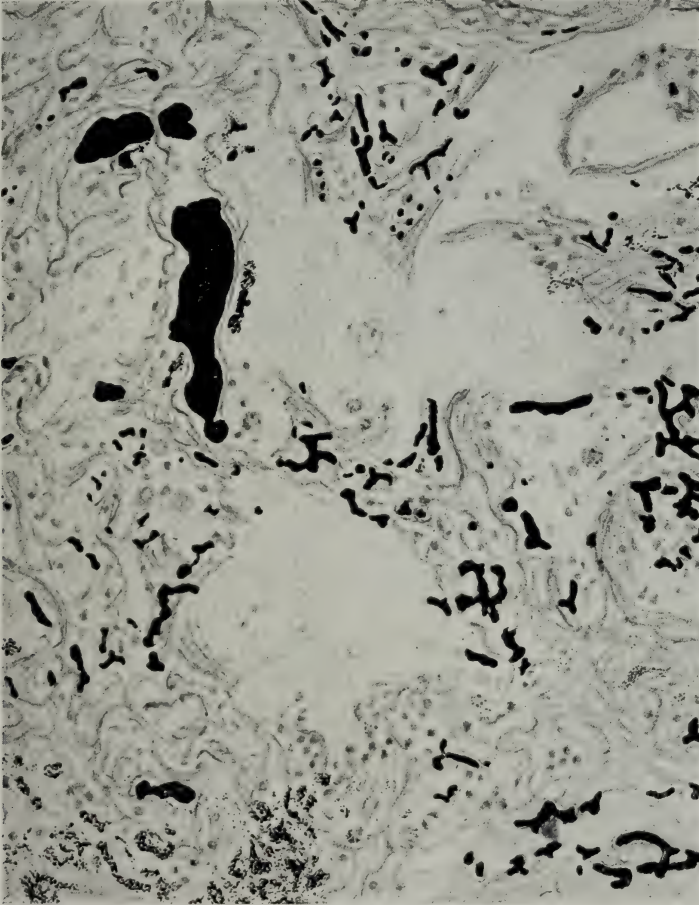


FIG. 56—Fat embolism of pulmonary vessels; stained with osmic acid.

indicated above, but the naked eye examination is likely to show little other than marked dilatation of the heart, particularly evident in the right side, extreme hyperemia and edema of the lungs. The dilatation probably depends upon the high pressure in the right heart and pulmonary circulation, incident to compensatory efforts to drive the emboli through the pulmonary circuit. The diagnosis depends upon microscopic examination with special stains for fat. In preparations of this sort the fat globules are found in the lung, in capillaries, smaller vessels and sometimes in the alveoli. In the kidney they are found particularly in the capillaries of the glomerular loops, but may be seen elsewhere.

In the heart, the capillaries exhibit the fat globules and the same is true in the brain. The presence of fat emboli in the stomach and in the brain may produce minute hemorrhages.

The fatal outcome of fat embolism depends upon the quantity of fat that gains entrance to the circulation. Simonds' study indicates that in the dog it requires about 2 cm. of oil per kg. of body weight to produce death, and this we find to be generally true in regard to the rabbit. In man, it is probable that other circulatory disturbances, incident to accident or operation, may make it possible for relatively small amounts of fat to produce a fatal outcome. Nevertheless, it is a common thing to find small quantities of fat in the lung in cases of fracture that meet death from other causes. It is not always true, however, that the appearance of a small amount of fat in capillaries is necessarily an indication of fat embolism, because Westenhoefer has found that putrefactive changes cause this appearance, and it is also known that the agglomeration of the fine fat particles in lipemia of diabetes may give the same appearance. If the patient survive, the fat is ultimately removed. The exact mechanism of this removal has not been finally established, but it appears that the calcium in the blood may saponify the fat and lead to its absorption, and that a certain amount may be removed by migrating phagocytic cells.

Air and Gas Embolism.—Provided the amount of air be sufficient, its entrance into the veins may lead to rapid death. The conditions in man, under which the air may enter, include surgical operations about the neck, shoulder and thorax, where the negative pressure may aspirate air into the large veins. Cases are recorded in which air has entered the venous system by way of the uterine veins following placenta previa, abortion, or after injections into the uterine cavity. It is considered by some that air may enter the gastric veins through ulcer of the stomach. Goodridge maintains that the anatomical relation of the jugular vein is such that, when it is incised it remains open and permits of ready access of air, but this is denied by Hare. No definite information is at hand as to the amount of air which must be taken into the veins, in man, in order to produce death, but in lower animals it is known that large quantities are necessary. Laborde and Muron injected 1120 cc. into the jugular vein of the dog, in an hour and a half, without causing death and even larger quantities are reported. These probably were large animals. In our own work we have produced death, in a dog of 10 kg., by the injection of 450 cc. in amounts of 20, 30, 50 and 70 cc. in the course of twenty-five minutes. The injection of 20 cc. gives a small fall in blood and pulse pressure from which recovery is rapid. The decrease of blood pressure is augmented by increases in the amount of air injected. A final injection of 70 c.c. produced a fall of blood pressure down to zero in the course of twenty seconds, and it was observed that respiration continued for three minutes after heart pulsation stopped. In the dog, the entrance of air into the heart is easily heard, with a stethoscope, as a bubbling sound and the same is said to be true in man. Physiologic studies show that with the fall in arterial pressure, the venous pressure for a time exhibits a distinct elevation. Although in man aspiration of

air into the veins is supposed to produce air embolism, nevertheless, this does not occur in the dog even when there is introduced into the vein a glass cannula to allow for ready access of air. The diagnosis of air embolism at autopsy depends upon careful technique. All the vessels leading to and from the heart must be ligated before the organ is opened. The organ is immersed in a vessel of water and an incision made into the right ventricle; air then bubbles up through the water. Unless these precautions be taken, air may readily enter the right heart during an autopsy and lead to confusing appearances. In true air embolism, the air is usually in the right ventricle and in the pulmonary arteries, down to the small branches. In these situations the air is found so mixed with the blood as to produce a foam. The heart is usually dilated, particularly on the right side, and in advanced cases there is considerable pulmonary edema. In some instances the air can actually be seen as bubbles in thin walled vessels. It is probable that a certain amount of air can be expelled through the pulmonary circuit into the general circulation, but this is not sufficient to produce serious damage, unless there be lodgment in important parts of the coronary or cerebral circulation. Couty attributed death entirely to failure of the right heart, which he thought unable to expel the frothy mixture with the same degree of efficiency as a fluid, because the froth is so easily compressible. More probable, however is the fact that air bubbles in a column of fluid lead to increased resistance.

Therefore, the presence of air bubbles in the column of fluid in the pulmonary vessels increases resistance to such a degree that circulation is retarded. This leads to an increased demand for work by the right heart, which cannot be met, and results in asphyxia, cerebral anemia and death. Death is cardiac in nature rather than respiratory. If the amount of air be small there may be no alteration of circulation, or there may be a slight fall of arterial pressure which is readily compensated. The air is removed by absorption.

Gases may be formed by bacteria, and it has been stated that these gas bubbles may produce embolism. The gas bacillus of Welch and Nuttall grows on dead tissues and although these organisms may gain access to the circulating blood, it is not probable that during life they produce gas in that situation. Therefore, gas embolism in cases of this sort must depend upon entrance of gas bubbles directly from the infected wounds into veins. In our experience with soldiers dead of gas gangrene, we were unable to demonstrate gas embolism.

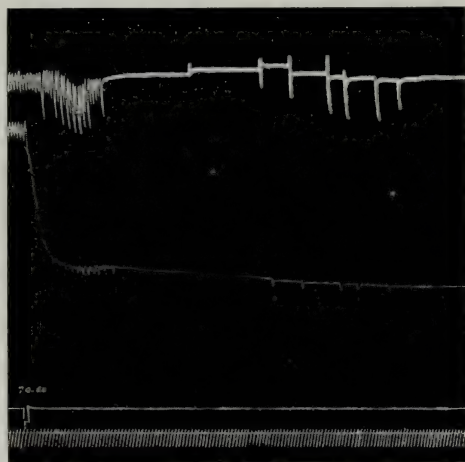


FIG. 57.—Tracing of air embolism in 5 kilo dog. Upper line shows respiration, middle line blood pressure in femoral artery. The lower lines are signal and time in 2 seconds. Before the final injection of 70 cc. air into femoral vein the animal had received 150 cc. in fractions of 10, 30 and 50 cc. Heart stops before respiration; the latter increases in depth and becomes gasping. The deep respirations record on the blood pressure tracing.

After death, provided the organisms be distributed by the blood, gas formation may be widespread in the body. These cases are likely to show foamy organs, a condition particularly well demonstrated in the liver but observed in practically all the viscera. Such changes, however, are only observed when the body has been dead for several hours at a proper temperature to permit of growth of the organisms. The organs are swollen, tense, soft, cut with diminished resistance, crepitate, show fine and large bubbles throughout. The condition may be produced experimentally by injection of organisms directly into the blood stream of an animal, killing the animal and allowing it to remain in a warm place for six to twelve hours.

Ordinarily included with gas embolism is the condition known as *caisson disease*. This occurs in divers and others who are obliged to work in atmospheres of compressed air. The high atmospheric pressure leads to increased absorption of gases by the body fluids, so that at a pressure of twenty-two pounds per square inch, the amount of nitrogen in the tissues may be more than doubled and the amount of oxygen and carbon dioxide also increased. When decompression occurs suddenly, the gases may be liberated in the form of bubbles in the tissues and in the blood. Nitrogen is liberated in greatest amount and usually constitutes most of the gas found, but carbon dioxide may also be present and it is believed that oxygen may be found. The bubbles in the tissues are of particular importance when they occur in the central nervous system, and their presence may lead to paralysis, sensory disturbances, coma and death. It is said that occasionally the amount of gas liberated in the blood stream may lead to fatal embolism.

A rare condition, known as *intestinal emphysema* or *gas cysts* of the intestines is occasionally observed. This, we believe, represents introduction of air or gas into the lymphatic vessels of the intestines, probably as the result of increased pressure of gas in the stomach or intestines. The gas or air enters the lymphatics of the gut through ulcers in the mucous membrane. Thus, it is essentially a gas or air embolism of the lymphatics. The symptoms may include abdominal pain, vomiting, sometimes diarrhea, and by x-ray study, upward displacement of the liver. The diagnosis is readily made on exploratory operation. The gas remains in situ for a considerable time and acts as a foreign body to induce a low grade inflammation in the surrounding tissues and the formation of multinucleated giant cells.

Hemorrhage.—Hemorrhage signifies the passage of blood from the blood vessels into any extravascular position. The hemorrhage, depending upon its origin, may be arterial, venous or capillary. When the blood passes outside the body, the condition is spoken of as external hemorrhage, whereas the entrance of the blood into the tissues or cavities of the body is called internal hemorrhage. *Petechiæ* or *ecchymoses* are hemorrhages in the tissues from 1 to 3 or 4 mm. in diameter. These are not infrequently referred to as purpuric spots. Sometimes the blood collects in the tissues in a fairly large, tumor-like mass, called *hematoma*. According to the origin of the hemorrhage various terms may be applied. *Epistaxis* signifies hemorrhage from the nose; *hematemesis* signifies vomiting

of blood; melena signifies the discharge through the rectum of blood, which originates from intestinal hemorrhage; hemoptysis signifies the coughing up of blood from hemorrhage in the lungs or respiratory tract; hematuria signifies blood in the urine; menorrhagia signifies profuse bleeding during the menstrual period, and metrorrhagia signifies bleeding from the uterus between periods; hematocolpos is a retention of blood or menses in the vagina; hematocele means accumulation of blood in a cavity, particularly that of the tunica vaginalis testis. Hemorrhage into the various serous cavities may be referred to, as hemothorax, when in the pleura; hemopericardium, when in the pericardium; hematocele, when in the tunica vaginalis. Bleeding into the brain is referred to as apoplectic hemorrhage.

According to the mechanism of extravasation, hemorrhage is distinguished

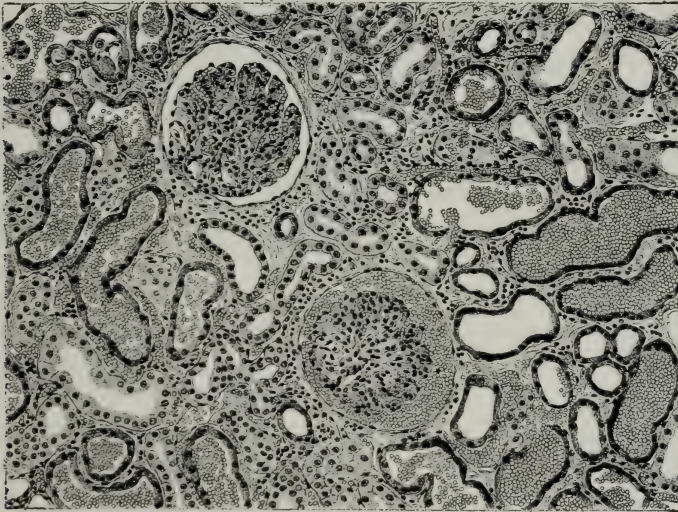


FIG. 58—Hemorrhage into a subcapsular glomerular space and into numerous tubules of the kidney.

as per rhexis and per diapedesis. Hemorrhage per rhexis signifies that form which results from rupture of the vessel wall. The rupture is usually traumatic as by wounds of various kinds, but may also result from erosion as by extension of ulcers. Disease of blood vessels may so alter their resistance to pressure that increases of pressure may lead to rupture, but it is hardly likely that any pressure can be present in the body sufficient to produce rupture of normal vessels, other than capillaries and vessels of almost capillary size. Such bleeding is seen in conjunctival hemorrhage resulting from vigorous coughing or violent vomiting. Diapedesis signifies the passage of relatively few red blood corpuscles through the vessel walls. In hemorrhage per rhexis all the blood elements and the plasma appear, but in diapedesis practically only red blood corpuscles are found. It has been thought that in diapedesis the red blood cells pass out through the lines of junction between the endothelial cells, but it seems likely that this is not altogether true, and that in certain if not all cases the red blood corpuscles pass directly through the endothelial cells as one colloid may

pass through another. The common example is the passage of a small globule of mercury through a column of soft gelatin, which passage is accompanied by no alteration, or after marks in the gelatin. Diapedesis is a very common accompaniment of passive hyperemia, occurring in the lungs, liver, and other organs. The destruction of the extravasated red blood corpuscles is responsible very largely for the pigmentation that accompanies prolonged passive hyperemia. Minute hemorrhages are also likely to follow the lodgment of emboli whether they be solid, liquid or gaseous, and the hemorrhage that is seen in infarction results from diapedesis in the earlier stages and probably from rhexis in the later stages. It must be said, however, that certain investigators consider that diapedesis rarely, if ever, occurs and believe that the small amounts of blood supposed to be the result of diapedesis are really from small points of rupture.

The hemorrhagic diatheses will be considered more fully in diseases of the blood, but it may be mentioned here that several diseases exist, in which hemorrhage plays a constant part. The hemorrhage is usually in the form of ecchymoses but may be more massive. These diseases include purpura hemorrhagica, and infectious and obstructive icterus, scurvy, hemophilia and others. Leucemias and pernicious anemia, as well as profound secondary anemias, may also be accompanied by hemorrhage. Whether the hemorrhage in these instances is due to alteration in the blood or alteration in endothelial lining of the vessels is problematical, but it seems likely that the latter is of importance in hemorrhagic anemias of various kinds, because of the lack of nutrition of these cells. Bacterial infection is not uncommonly a cause of hemorrhagic tendencies, as exhibited in cases of streptococcus and staphylococcus septicemia, as well as in such specific infectious diseases as anthrax, plague, etc. It is now known that infectious icterus is due to a spirochete, the *spirocheta icterohemorrhagica*, and therefore this disease cannot be regarded as bacterial. Certain poisons such as phosphorus, some of the snake venoms, and poisonous fungi, may also in their action on the body be accompanied by hemorrhages, and this is now believed to be due to a direct specific action upon the capillary endothelium so as to permit the extravasation of blood. Phosphorus and chloroform poisoning are accompanied by a reduction in fibrinogen, and this alteration in the blood reduces its clotting capacity so as to favor continuance of hemorrhage. As has been indicated, passive hyperemia is an important condition in the production of certain forms of hemorrhage, and it is possible also that depression of vasomotor activity may lead to circulatory disturbances, which in their turn accentuate a tendency to hemorrhage. Hemorrhage appears frequently in the inflammatory reaction, and is discussed further in that connection.

The sequences of hemorrhage depend upon the amount of blood lost, the situation of the hemorrhage and numerous other factors. As has been pointed out previously, a considerable amount of blood may be lost without producing death. This leads to a temporary secondary anemia which may readily be recovered from. Multiple small hemorrhages prolonged over long periods of time, may lead to profound secondary anemias. Hemorrhage may appear in certain important situations as for example in the brain, and lead to paralysis and even

death. In the pericardium its presence alters cardiac activity and may be fatal. The presence of blood in the tissues operates in the same way as a foreign body. The changes in the blood itself are somewhat similar to those seen in thrombosis, but in extravascular positions the corpuscles more rapidly undergo degeneration and die, with secondary changes in the blood pigment. In the margin where there is a certain amount of access of oxygen, hemosiderin is formed, whereas in the center hematoidin may be observed. Leucocytes and endotheliocytes penetrate only a limited distance into the margin of the hemorrhage, phagocytose the hemosiderin and remove it to the surrounding living tissue. A moderate amount of transport may occur to the neighboring lymph nodes. The fact that the blood acts as a foreign body, leads to a fixed tissue reaction in the neighborhood, so that fibroblasts and capillaries appear with the ultimate formation of adult connective tissue. If the hemorrhage be small, this adult connective tissue may entirely replace it, but if it be fairly large the connective tissue forms a capsule and the softened blood appears as a cyst. Blood pigment usually gives to the contents of this cyst only a light yellow color, because most of the pigment is removed by diffusion and by the action of phagocytes. Bile pigment may also be formed. The margins of such areas, however, are likely to be deeply pigmented because of the presence of the hemosiderin contained in the phagocytes.

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CHAPTER VIII

INFLAMMATION

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- INFLAMMATION IN AVASCULAR TISSUES.
- ULCER.

Introduction.—There are many features in the normal structure and physiology of the body which serve to protect against injury. The continuity of skin and mucous surfaces protects to a considerable extent against minor injuries. The structure of bones is such as to resist injury, and the conformation of such bony structures as the skull, thoracic cage and pelvis are especially adapted to protect the organs within them. Normal or increased secretion,

such as of the eyes, nose, urinary tract; movements, such as of the eyelids, or cilia of the tracheal mucosa; chemical constitution, such as of the gastric juice, are other instances of natural defense mechanism against injury or bacterial invasion. Reflexes such as sneezing, coughing, dodging, are definite protective mechanisms. There are also, within the body fluids, certain substances called immune bodies, which may be increased by survival of natural disease and by artificial processes. These endow the organism with an important means of defense.

Inflammation, however, is a local process, distinct from the structural and physiological mechanisms indicated above, and only to a limited extent participated in by the humoral defenses. It may be associated with general changes such as fever, leucocytosis and development of immune substances, especially when it is caused by bacterial infection, but in itself operates only at the site of injury. Much discussion has appeared in the literature as to the definition of inflammation and some recent writers have declared that it cannot be defined. Nevertheless, the process is established in response to injury, and is followed either by healing and restoration, or by extension and death. Before giving a definition it may be well to describe the process.

The primary injury, which leads to death of a few cells or a more extensive area of necrosis, may be physical (including circulatory changes), chemical or bacterial in nature. Although there is some difference of opinion, it seems improbable that the reaction of inflammation may occur unless it follow actual death of cells or tissues. Depending upon the cause and upon the resistance of the body, the course, duration and ultimate results of inflammation vary. Fundamentally, however, the primary reaction affects the vascular structures, followed very soon after by reaction in the fixed tissues, and finally, provided the reaction be successful, there is complete repair of the lesion. The changes which occur in blood vessels affect the smaller arterioles, the venules and the capillaries. The exact nature of the first change visible in these vessels is not finally and definitely known, but it is generally believed that there is, at the beginning of the inflammatory process, a minor and evanescent constriction of these small vessels. This is followed by a more lasting dilatation. During the period of constriction, blood flows with increased rapidity, and this persists for some time after the beginning of dilatation. Subsequently the blood flow is decreased in rate, a change which may go on to complete stagnation of the current. Examination of the blood as it flows through the vessels shows that there is normally a central zone or current, which contains the blood corpuscles known as the axial zone, and in addition there is, between the corpuscles and the vessel walls, a small zone containing plasma, called the peripheral or marginal zone. These zones are maintained by the vortical force acting upon the heavy cells as compared with the lighter plasma. In the early stages of inflammation when the circulation is normal or increased in rate, these two zones are clearly defined. As circulation is slowed, however, the lighter corpuscles, namely, the white blood corpuscles, because of their lower specific gravity, appear in the peripheral zone. During this stage, the leucocytes may

be seen to adhere to the vessel walls and finally, by ameboid movement pass through the walls and appear in the surrounding tissues. They may then migrate further into the tissues toward the point of injury. At the same time the fluid of the blood passes through the vessel wall and appears in the tissues. In this extravascular position the plasma, or a fluid closely resembling plasma, coagulates to form fibrin and serum. Red blood corpuscles also pass through the vessel walls, probably by virtue of the fact that one colloid may pass through another colloid, provided there be certain differences in density and specific gravity. The passage of the leucocytes is spoken of as migration or emigration; that of the red corpuscles as diapedesis, and that of the fluid as exudation (in the narrower sense). As a matter of fact, the term exudation covers the passage of all these substances through the vessel walls to the tissues. If the slowing of the blood current go on to complete stagnation, the distinction between peripheral and axial zones is completely lost.

The essential element in the reaction of the fixed tissues to the injury, is the proliferation of fixed tissue cells including particularly the connective tissue cells. Very shortly after the new connective tissue cells, or fibroblasts, begin to appear, the endothelium of the smaller blood vessels proliferates so as to form new capillaries and new small blood channels of various diameters. The proliferation of capillaries and of connective tissue may be sufficient to fill completely the destroyed area. Subsequently, the capillaries undergo atrophy and disappear, and thus the cicatrix or scar is formed. The actual regeneration of cells or cellular structures to replace those that have been destroyed, varies from complete absence of regeneration in the highly specialized nerve cell, to a considerable regeneration of the less highly specialized liver cell. Regenerative capacity varies greatly under different conditions and this capacity will be discussed subsequently.

Definition.—The processes involved in the foregoing outline include the cause of the injury, the nature of the injury, the vascular reaction, exudation, removal of injurious and destroyed substances, tissue and vascular proliferation, regeneration (if any) and cicatrization. Old definitions were based on the cardinal symptoms which will be mentioned subsequently, and the term inflammation was derived from one of these symptoms, the increased temperature or heat of the part. Definitions based on symptoms and signs obviously are not concerned with the intimate nature of the process. Clinical definitions have sometimes been limited to that part of the process which ends in pus formation, especially when caused by bacterial infection. Nevertheless, a process inaugurated by bacterial infection, for example acute meningitis, may show on one day a serous exudation and on the next exhibit pus, but the fundamental nature is unchanged. The principle difference of opinion among pathologists and biologists in general, has centered about the questions: (a) as to whether or not the primary injury can be considered a part of the process, (b) as to the limitation of the definition to the vascular reactions and consequent exudation, and (c) as to the inclusion in the process of fixed tissue proliferation, repair, regeneration and cicatrization. Certainly, the primary injury is in most

cases a condition or stage of degeneration or death and is not truly a part of the defensive reaction. It is, however, intimately bound up with the reaction, which follows immediately. From the dynamic viewpoint the vascular reactions represent a physiologic change, possibly in response to more or less definite stimuli, and constitute beyond doubt a physiologic process adapted to pathologic needs. Certain excellent authorities exclude the tissue proliferation as not representing a reaction which is *per se* of defensive character. It must be admitted, however, that cell reproduction represents a response to stimuli, whether of a vague biological nature or of the more precise physico-chemical nature indicated by J. Loeb. Furthermore, in inflammation there is no sharp demarcation between the period of vascular reaction and tissue proliferation; the one stage merges gradually into the other and the two may co-exist for long periods. Exudation may exceed the needs of the organism and become excessive; tissue proliferation may do the same. Regeneration, however, practically never exceeds the requirements of replacing a loss. Regeneration might be excluded on this ground, but it is also intimately connected with inflammation. A further point of discussion concerns the inclusion of certain lesions of parenchymatous viscera, in which the degeneration of the parenchymatous cells dominates the picture. An organ may be the seat of degeneration without any signs of inflammation, but if there be exudation or tissue proliferation as a part of the local process the name inflammation or as Marchand suggests, inflammatory disease, is justified.

It is, therefore, possible to accept under the heading of inflammation either a definition limited by agreement, or to include various stages or all stages of the defensive and reparative mechanism. We modify the definition of Marchand so as to include in inflammation all the phenomena observed from the time of injury to the time of repair, thus including a series of reactive processes in the vessels and tissues, which follow upon injuries of physical, chemical or infectious nature, run a more or less regular course, and, in favorable cases, result in the destruction and removal of the injurious substances and lead to repair and healing. Beitzke emphasizes the defensive, self-regulatory and progressive features of the process.

Cardinal Signs and Symptoms.—The gross manifestations of inflammation have been clearly known since the time of Celsus, who pointed out four cardinal signs of the condition, redness, swelling, heat and pain (rubor, tumor, calor, dolor). As a result of later studies, a fifth cardinal sign, disturbance of function (*functio laesa*), was added. John Hunter particularly emphasized the fact that this is a process which attempts to counteract the injury which induces the reaction. Cohnheim, by observation of the web of the frog's foot through the microscope, studied the actual progress of acute inflammation. Observing the alterations of vessels and blood flow, and the passing of fluid and cells through the walls, he was able to explain many of the factors underlying the cardinal signs and symptoms. Metchnikoff studied the phenomenon of phagocytosis and emphasized its importance in inflammation. As one of the most general and important pathological processes, this subject has been stud-

ied by a large number of investigators, and the contributions of such great investigators as Cohnheim, Leber, Councilman, Adami, Thoma, Ribbert, Klemensiewicz, Marchand, Aschoff and numerous others have been of such fundamental nature that the process can now be interpreted on a rational basis.

Classification.—Inflammation shows variations depending upon the nature of the injury, the presence of diffusible substances, the violence and duration of reaction, the capacity for reaction and repair, and upon certain other factors. It is possible to classify the process in a variety of ways. Simplest perhaps is the division into acute and chronic inflammation depending particularly upon the duration of the process. Finer shadings of meaning are indicated by the terms subacute, of longer duration than acute, and subchronic, of shorter duration than chronic. Inflammation may also be classified according to the nature of the exudate, so that it may be regarded as serous, fibrinous, purulent, hemorrhagic, or catarrhal in type, or the exudate may be so constituted as to require combinations of these terms for descriptive expression such as serofibrinous, fibrinopurulent, etc. It must be understood, however, that all exudates contain various blood elements and that the use of any of these terms simply indicates a preponderance of one or more types of constituents. Another classification depends upon the essential nature of the process upon microscopical examination. Alterative inflammation signifies an inflammation in which the degeneration of the tissues constitutes the major part of the picture. Exudative inflammation indicates a process in which fluid and cellular constituents predominate. Productive or proliferative inflammation indicates that the multiplication of fixed tissue cells constitutes the most striking part of the process.

Causes of Inflammation.—Since inflammation is a reaction to injury, the causes must be sought among injurious agents. The most tangible evidence of injury is local death or necrosis of tissue, and therefore the causes of necrosis are also causes of inflammation. Rössle has found that many protein disintegration products in practically pure state may induce inflammation. It is possible, however, that certain forms of inflammation, particularly those grouped under the heading of alterative or degenerative inflammation, may be caused by injuries which produce retrogressive changes in the tissues not necessarily leading to cell or tissue death. Thus, certain inflammations of parenchymatous organs may be induced by circulating poisonous substances which are not of sufficient virulence to produce actual death of the cells, but lead to the less severe cloudy swelling or fatty degeneration. The causes of necrosis have been enumerated in the chapter on necrosis. They may be physical, such as mechanical injury; lesions due to electricity and light; thermal; the chemical corrosive poisons; the toxins or other poisonous substances produced by bacteria; poisonous substances produced by abnormal metabolism and certain types of poisons introduced from without; circulatory disturbances, particularly complete occlusion of a supplying artery; and such neurotrophic disturbances as may lead to death of the tissues. In so far as acute inflammation is concerned, the most important of all causes is bacterial

infection. Pyogenic organisms, the pus producers, are among the most frequent causes of acute inflammation. Nevertheless, numerous other organisms may excite acute inflammation including the pneumococcus and other organisms of that group, the diphtheria bacillus, the bacillus pyocyaneus and numerous others. The colon bacillus is one of those organisms which occupying certain positions, as for example, the intestinal canal, does no damage, but when implanted in other situations may serve to produce severe inflammation. Bacteria may gain access to the body through any of its surfaces including the skin, and the mucous membranes of the respiratory, alimentary and genito-urinary tracts. Protection is afforded against entrance by the continuity of these surfaces, by secretions, movements of secretion, constitution of secretion, and other protective mechanisms. Organisms vary considerably in virulence and may lodge in situations only to be discharged in various ways. If virulence be sufficient, the lodging of organisms in the body may readily lead to inflammation. A common example is the lodging of bacteria in the hair follicles of the skin, where their growth and multiplication not infrequently gives rise to minute or even very large abscesses. Lodgment in tissues about the teeth or in the crypts of the tonsils, or in other situations where removal is difficult, gives rise to similar manifestations. If the inflammation be not sufficiently pronounced to prevent further dissemination of the bacteria, they may be transmitted to other parts by the lymphatic current or by the blood stream. They may thus lodge in lymph nodes or in finer divisions of the blood vascular tree and set up secondary foci of inflammation. Bacteria in their growth produce certain poisonous substances which because of their diffusibility may result in necrosis of the surrounding tissue. Parasitic organisms may grow in living tissues and lead to death in the immediate neighborhood. In the case of saprophytic organisms a preëxisting area of dead tissue is necessary, but following their growth, necrosis in surrounding tissue may ensue.

When organisms gain access to the blood stream, they may be destroyed by bactericidal substances in the blood or may be ingested and destroyed by leucocytes and vascular endothelium. They may, however, survive and lodge in such situations as to occlude capillaries or small arteries, obstruct circulation in these areas and produce necrosis because of local circulatory deficiency. This local area of death provides for further extension of bacterial growth, because it is an excellent culture medium and within it the normal defenses against bacterial growth are decreased or inoperative. The soluble poisonous substances produced by bacteria may be diffused rapidly and widely throughout the body, and if in sufficient concentration may excite low grade alterative or degenerative inflammation in parenchymatous viscera. An excellent example of this phenomenon is the case of diphtheria. Infection by the diphtheria bacillus leads to a local inflammation in the fauces, the nose, the larynx or occasionally in some other situation. Although the local manifestations may not be extremely severe, yet the organisms produce a soluble toxin, which is absorbed and passes through the body in the blood and body fluids. This acts upon the tissues so that acute inflammations of such parenchymatous viscera as the

kidney, heart and liver are commonly produced. On the other hand, bacteria may be present in the circulating blood, and, because of relative failure to produce toxic substances, do little harm. In the lower animals bacteria are without doubt frequently present in the circulating blood. The work of Wolbach and Saiki, referred to in the discussion of autolysis and confirmed in our experience, demonstrates the difficulty in securing a section of liver in the dog or cat, which upon subsequent cultivation will not show bacterial contamination, and it is a safe inference that the bacteria are transported to the liver by the blood stream. It also seems probable that in man there are frequent instances where bacteria appear in the blood stream but do little or no damage. Adami calls attention to the fact that bacteria are very frequently taken into the system from the alimentary and respiratory tracts, and that they are ultimately destroyed by cells and other defensive mechanisms with which they are brought in contact. He suggests the name *subinfection* for this condition. It is often difficult, however, to draw a sharp line of distinction between subinfection with no clinical manifestations and mild infection with very slight manifestations.

Mechanical injuries of various kinds may lead to inflammation. In fact, the production of a wound under strictly aseptic conditions results in minor degrees of inflammation. Under less favorable circumstances, mechanical injury serves often as a ready means of access for bacteria. Thermal injury may result in burns varying in degree from a slight reddening of the skin to severe burns with actual destruction of deep tissues; in response to all these there are different degrees of inflammation. The death of parts as the result of exposure to cold leads to inflammatory reaction in the surrounding living tissues. Burns by the electric current also produce injury with inflammatory reaction. The influence of light is manifested in sunburn. It has been pointed out that the tissues may be sensitized so that the reactions to light may be more severe. The use of radium and of roentgen rays produces, if the dose be sufficiently large, injury and necrosis of tissues which, in the form of the so-called burn by these agents, shows the inflammatory reaction. Chemical corrosives may lead to immediate death of the entire organism, but if the application be local, the destruction of tissues is rapidly followed by inflammation. Of the toxic substances which may produce inflammation, the bacterial poisons are of the utmost importance. Metabolic poisons probably are active in such disease as gout, chronic rheumatism and the like. Poisons introduced from without include lead, arsenic, mercury, and possibly alcohol, tea and coffee. Certain of these materials may produce actual necrosis of parenchymatous tissues, as is well exemplified in the case of mercury bichloride, but the injury from many of the exogenous poisons is minor in degree, and only after prolonged administration leads to subacute and chronic inflammatory reactions in various tissues of the body. If circulatory disturbance be not complicated by bacterial infection, the inflammatory reactions are relatively slight. For example, the reaction to the presence of a bland infarct is usually moderate in degree. Similarly, chronic passive hyperemia may lead to a low grade chronic

inflammation in the parts, which sometimes goes on to very marked proliferation of connective tissue. Neurotrophic disturbances may apparently lead to necrosis and result in reactive inflammation, but since these neurotrophic disturbances are often accompanied by disturbances of sensation, it seems likely that the resultant traumatic injury and access of bacteria are of more significance than the nerve lesion.

Vascular Changes in Inflammation.—As has been indicated above, the immediate and primary change in the smaller blood vessels in inflammation is a matter of controversy, but it is generally accepted that there is a primary and evanescent constriction of the vessels. This is rapidly followed, however, by a more lasting dilatation of the vessel. As a result of this dilatation, the arterial pressure is more directly communicated to the small vessels than is true when their calibre is normal. Hence, the rate of flow in the small vessels is accelerated. Klemensiewicz found an increase in arterial pressure in the early stage of inflammation in the leg of a dog from 174 to 190 mm. mercury, which could increase the rate of flow in the inflamed capillaries above that of a normal physiological active hyperemia. The pressure is probably communicated through the capillaries to the veins, for the capillary and the venous pressure is also increased. The increased rate of flow persists, however, for only a short time and is replaced by a slowing of the current, which may progress to complete stagnation. If stagnation persists, clotting occurs. Although Greenfield and Lyon maintain that the dilatation appears first in the veins and capillaries, most observers agree that the dilatation appears first in the small arteries and arterioles and subsequently in the small veins, venules and capillaries, a conception more nearly in accord with the known anatomical and physiological facts to be discussed. The chief problems to be dealt with are the mechanism of the vascular dilatation and the manner of slowing of the blood current.

Although the vascular dilatation is essentially an active hyperemia, yet there are important differences between inflammatory and simple active hyperemia. Adami would emphasize the difference by using the term capillary hyperemia for that occurring in inflammation. Samuel pointed out many years ago that if hyperemia of the rabbit's ear be produced by constriction at its base, puncture of the ear between the larger visible vessels leads to no hemorrhage, but if the ear be inflamed, puncture in the same situation leads to profuse bleeding. An important difference was also pointed out by Meltzer and Meltzer, who found that the injection of adrenalin into a rabbit's ear, the seat of inflammation, produces no effect, whereas similar injection into an ear the seat of simple active hyperemia produces immediate pallor. Another difference of importance is that in ordinary active hyperemia the blood flow is continuously accelerated, whilst in inflammatory hyperemia the blood flow is only temporarily accelerated and for the most part delayed. Inflammatory hyperemia is likely to be of much greater duration than is ordinary active hyperemia. These differences may have an important bearing upon the fact that inflammatory hyperemia results in exudation, whereas ordinary active hyperemia does not. Of some importance is an understanding of the anatomy of the small vessels. Hooker

points out that the arterioles are provided with a distinct muscular wall, and that the musculature continues for a certain distance along the arterial segments of the capillaries. They are then devoid of musculature until they enter into the venules, which latter possess a musculature relatively less in amount than the corresponding arterioles. Nerve terminals almost certainly of motor type are found in connection with this smooth muscle. Nerves are found in the tissues in which the capillaries are embedded, but there is no clear and final indication that these communicate with the capillary endothelium. After extensive personal study and a careful review of the literature, Hooker concludes that, in a broad sense, chemical factors influence the dilatation of the capillaries and the venules, whereas nerve stimulation influences the constrict-

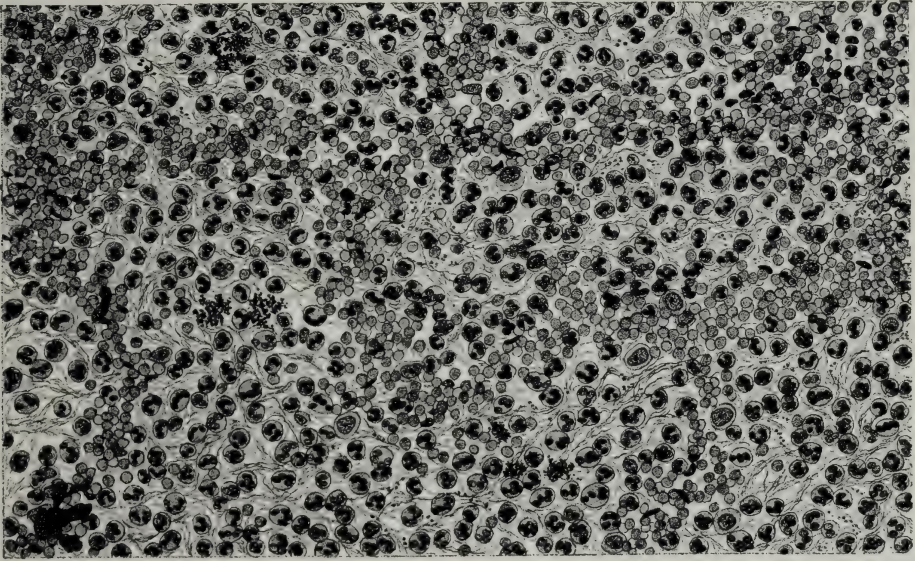


FIG. 60—Capillary hyperemia in early pneumonia. Alveolar outlines are vaguely marked by the masses of erythrocytes within the capillaries. The alveoli show leucocytes, fibrin and bacteria.

tion of these vessels. There is little doubt that nervous influences control the calibre of arterioles and probably also of the arteriolar segments of the capillaries. The chemical influences operative in the early stages of inflammation probably are of minor importance, although there is little doubt that as soon as tissue necrosis occurs the reaction of tissue and tissue fluid changes toward the acid side. Krogh has found that among other chemicals which may induce dilatation of capillaries and enlargement of the capillary bed, are acetic and carbonic acids. In experimental inflammation the dilatation is observed within a very few seconds after injury, and whether alteration in reaction, due to death of tissues, or an overproduction of carbon dioxide from increased metabolism, occurs in this short space of time seems questionable. Nevertheless, there is no reasonable doubt that these influences may serve an important purpose in maintaining the dilatation of the capillaries. By the use of trypan blue, Hirschfelder demonstrated injury to the capillary walls. The question of the

regulation of the inflammatory reaction by the nervous system has been the subject of many investigations. Samuel cut the sympathetic nerve supplying one ear of the rabbit and the auricular nerve of the other ear. Division of the sympathetic led to vasodilatation, and of the auricular to vasoconstriction. Both ears were then placed in water at 50° C. The ear in which capillary dilatation was present went on to severe inflammation, whereas that in which vasoconstriction was present responded much more slowly. Meltzer and Meltzer also found that an ear from which the sympathetic control had been removed, responded somewhat more violently than a normal ear. It is there-



FIG. 61—Inflammatory edema of rabbit's ear, due to painting of one surface with croton oil. The marked swelling of the painted side is contrasted with the slight swelling on the opposite side of the cartilage. Note the capillary dilatation, the marked separation of tissue fibrils by edema and the relatively slight cellular exudate.

fore possible to influence inflammation by manipulation of the nervous control. Adami points out that during hypnosis, inflammation may be produced without any local injury. For example, in the hypnotic subject suggestion is so powerful that if a cold coin be placed near the skin and the subject informed that this coin is hot enough to produce a burn, local inflammation may result. Bruce calls attention to the reverse condition in hysteria, in which the application of a real irritant to the skin may not be followed by inflammation. Head and Campbell investigated herpes zoster, a condition in which inflammatory vesicles occur over the course of peripheral nerves. They observed lesions of the spinal root ganglia of the sensory nerves and attributed the herpes to these central disturbances. Bruce also calls attention to sympathetic inflammation wherein irritation in one nerve may lead to signs of inflammation

in areas supplied by closely associated nerves. He offers as an example the instance in which a toothache may be accompanied by redness, swelling and pain on the same side of the face. Much interest was excited by the work of Bruce, who came to the conclusion that the primary vascular reaction is due to an axon-reflex. Motor stimulation in vascular areas through sensory nerves has long been known through the work of Sakowin, Langley, and Anderson and Bayliss. The term axon-reflex is used to indicate passage of stimuli through an arc composed only of nerve terminals, and is declared to be general for the vasomotor and sympathetic systems. The nerve is regarded as having a bifurcated extremity. A sensory impulse may be transmitted centralwise along one branch of the fork, meet the main stem and then pass peripheralwise,

in the antidromic sense of Bayliss, along the other branch. Bruce pointed out, as has long been known, that a reflex arc with connections in the central nervous system is not involved in inflammation. He studied the problem by the use of local anesthetics which paralyze sensory nerve terminals, by section of nerves and by degeneration of nerves following section. He declared that peripheral anesthesia inhibits inflammation. He also stated that so long as nerve degeneration does not involve the axon-reflex arc, inflammation occurs, but that after the terminals have degenerated, inflammation is inhibited. Confirmation of his views was offered by Januschke and by Groll. Stevenson and Reid, however, found that neither local anesthesia nor degeneration of sensory terminals has any demonstrable effect on inflammation, and on the basis of animal experiments and observations on human patients, contradict the conclusions of Bruce. In their experiments with degeneration of the fifth nerve, however, they did not protect the eye against injury. Hirschfelder finds that any inhibition produced by local anesthetics is due to their power of vasoconstriction. Ebbecke objects to the axon-reflex as applied to inflammation, in that the vasodilatation is too long maintained to be of reflex origin, and further that the reaction appears in areas where there are no sensory nerves. Breslauer obtained results similar to those of Bruce, but considers that the vasodilatation is much more likely to be a direct action of irritant upon innervated parts of the vessel wall, or upon the end-organs of these nerves. In view of the more recent studies it seems fair to conclude that the differences between inflammation in otherwise normal and in denervated parts are at the most only quantitative and do not concern the fundamental nature of the process. The dilatation is often seen first in the arterioles, vessels with a neuromuscular supply, and it is at least possible that a nerve influence is concerned. On the other hand, the dilatation is prolonged over hours and days and it is unlikely that vasomotor activity would continue for this time. Klemensiewicz as well as Marchand and numerous others are convinced that the vasodilatation is paralytic. Even admitting that nerve activities may be of temporary importance, the prolonged dilatation, especially in view of the work of Stevenson and Reid, of Ebbecke and of Breslauer, cannot be so explained.

If nerve influences be excluded, the paralytic effect must be directly upon the vessel walls, and due to some substance or substances generated in the inflamed area. Of the various substances that might be operative, carbon dioxide deserves first mention. Cohnheim regarded the injury as due to lack of oxygen, which at the present time might indicate excess of carbon dioxide. Wells quotes Gaskell as demonstrating that vascular muscle undergoes atonic dilatation in the presence of excess of carbon dioxide, and as has been indicated, Krogh found that this acid produces capillary dilatation and enlargement of the capillary bed. The work of Dale and his collaborators shows that histamine, a derivative of histidin, which may be formed in the course of tissue destruction, acts directly as a capillary poison and produces dilatation of capillaries with an increased per-

meability of their walls. Rich has shown by exact measurement the dilatation of preëxisting capillaries, and the opening up of numerous capillaries which otherwise were closed; the capillary bed is increased. It is not possible at the present time to state finally that histamine or some similar substance is the cause of the local vasodilatation of inflammation. Of further interest is the fact pointed out by Amberg, Loevenhart and McClure that an increased amount of oxygen, rendered available for the tissues by injecting sodium salts of o-iodoso- and o-iodoxy-benzoic acid, inhibits inflammatory reactions. This supports the Cohnheim theory that decrease of oxygen in the part is an important cause of vasodilatation, by virtue of the consequent deterioration of the vessel walls. There can be little doubt that other injurious substances may be generated in the injured part, for it is known that a considerable number of substances may cause vasodilatation. Vasodilatation, however, is observed in the frog's mesentery in a time so short after injury that it may be measured in seconds rather than minutes, and it is doubtful that this can be due to lack of oxygen, accumulation of carbon dioxide, or production of capillary poisons. It therefore seems probable that the primary vasoconstriction and the earlier stage of vasodilatation are due to nervous influences, and that the prolonged dilatation, paralytic in nature, is due either to decrease of oxygen, increase of carbon dioxide, production of substances poisonous to the small vessels, or a combination of these factors.

The slowing of the blood current has been attributed to various influences including alteration of the viscosity of the blood, swelling of the vascular endothelium, or an obscure increase in stickiness or diminution in smoothness of the vessel lining. There can be no doubt that if the proper physical conditions be present at the beginning to establish increased rate of flow, the subsequent decrease of rate must be due to local changes. Wooley, after a careful study of the literature, comes to the conclusion that the decrease in the rapidity of the blood stream is the result of two factors; namely, an increase in the volume of the cells of the blood and of the endothelial cells lining the blood vessels, and increased viscosity of the blood as a whole. The evidence to support these conclusions is abundant and important. It must be obvious that the local activities in inflammation produce increased rate and volume of metabolism. Therefore, it is to be presumed that the products of metabolism are present in increased concentration. The presence of these products, particularly carbon dioxide, lactic and other acids has been called upon to explain the permanence of capillary dilatation. Studies of the red blood corpuscles indicate that an increase in the carbon dioxide content increases the size of the corpuscles. This fact has been pointed out by numerous physiologists, and probably depends upon the increased hydrophilic character of the protein of the red blood corpuscles, incident to the increase in carbon dioxide content. The same general principle applies to the increase in size of endothelial cells, whose intimate relation to the surrounding tissue affords a ready access not only of the carbon dioxide but also of fixed acids such as lactic acid, which combining with the protein of the cells increases the hydrophilic properties and

therefore leads to swelling. It is indeed possible to observe this swelling of endothelial cells during the period of increased rapidity of blood flow, followed in a short time by a slowing of the blood current and continued increase in the size of the lining cells. It is well known that the addition of acids to protein causes a swelling in the protein due to imbibition of water. The proteins of the blood fluid are no exception to this rule, and it may be readily assumed that as the plasma becomes increasingly hydrophilic, there is a resultant increase in viscosity. Nevertheless, it must be conceded that although endothelial cells are swollen, there is no reason for believing that there is any marked difference in the character of the cell walls, and therefore no good reason for believing that the slowing is due to stickiness of the lining cells in the ordinary sense of the term. It is possible, however, that the alteration of the reaction of the cytoplasm and cytoplasmic fluids may, by virtue of altered surface tension, have some attraction for the cells of the blood and perhaps also for the fluids. Increase in viscosity of the blood may also be due in part to the fact that fluid exudes from the vessels early in the reaction, thus providing an increased concentration within the vessels. Klemensiewicz offers a different explanation for slowing of the blood current, which in our opinion is not given due weight by Wooley. Klemensiewicz points out that as fluid accumulates in the tissue, its hydrostatic pressure may exceed the hydraulic pressure in the venous segments of the capillaries, and thereby produce a constriction of these capillary terminals and small venules, which of course would dam back the blood in the arterioles and arteriolar segments of the capillaries. This will be referred to in the discussion of the fluid of the exudate.

As the current is slowed there occurs a change in the character of the blood column. The differentiation between peripheral and axial zones is decreased and may be entirely lost. In the earlier stages of this change the first thing noticed is the appearance of leucocytes in the peripheral zones. It is perfectly reasonable to suppose that the blood cells maintain a central position in the blood current, because of the vortical or centripetal force of the flow of fluid in the tube. Quite naturally, therefore, it would be expected that if this vortical force be reduced by slowing of the current, the first particles to separate into the outer zone of the stream would be the lighter ones and these, in the blood, are the leucocytes. It is possible also that those chemical influences which as will be explained subsequently, serve to attract leucocytes into the surrounding tissue, may also play a part in their marginal position. These cells attach themselves to the lining endothelium of the vessels, and by the force of the blood current may become somewhat elongated. The actual attachment of the leucocytes is not clearly understood but it may well be due to lowered surface tension, both of the leucocytes and endothelium, induced first, by the changes in character of the endothelial protoplasm and second, by subsequent similar changes in the leucocytes themselves.

Exudation.—Very shortly after dilatation of the smaller blood vessels is observed, the process of exudation begins. By this process, the solid and fluid constituents of the plasma as well as the blood cells pass through the vessel

walls and, situated within the tissues, constitute the exudate. It is important to know the elements which make up the exudate, the factors which alter the nature and proportions of these constituents, the mechanisms by which they pass out of the vessels and the purposes which they serve in the process of inflammation.

The Fluid of the Exudate.—In most examples of inflammation, the material which first passes through the vessel walls is fluid. It originates from plasma and is coagulable, but differs from plasma in several respects. The appearance of a blister in the skin following a burn exemplifies how rapidly the fluid exudate may accumulate. The production of this fluid probably depends upon fundamentally the same mechanism as that of the formation of lymph, but there are important differences. The difference in rate of formation and essential constitution is indicated in the experiment of Samuel, who studied the lymph flow from the foot of the dog. In a normal control he recovered, during three hours, 4.0 cc. of lymph, containing 4 to 5 per cent. of solids. From a foot the seat of passive hyperemia he recovered 28.5 cc. lymph, containing 2 to 3 per cent. solids. From an inflamed foot he recovered 28.5 cc. lymph containing 7 per cent. solids. The specific gravity of inflammatory exudate is considerably higher than that of edema fluid from passive hyperemia or that of normal lymph. According to Halliburton, the specific gravity of exudate is 1020 or higher, whereas that of mechanical forms of edema and that of normal lymph is considerably lower than these figures. The main reason for the increase of specific gravity is the presence of large quantities of serum globulin and serum albumin. The fluid of the exudate contains practically all the solid constituents of the blood plasma, but their concentration shows certain differences. In addition, the fluid of the exudate contains materials contributed from the inflammatory tissues. Thus, the inflammatory fluid contains salt in very much the same concentration as the plasma, extractives of various kinds including urea, fibrin forming elements, soaps, mucin, ferments and immune bodies. Oxidases, lipase, and trypsin are found. Antiferment is also present, as in the plasma, but frequently the proteolytic ferment contributed by the cells of the exudate not only neutralizes the anti-ferment but may be present in excess. All types of immune bodies may be found including cytolytins, hemolytins, bacteriolysins, agglutinins and opsonins, as well as complement fixing bodies. Complement is also present but in extremely variable amounts; it is particularly likely to be low in amount if the exudate be rich in leucocytes (pus). As a rule, the ferments and immune substances are distinctly higher in inflammatory edema than in edema from other causes.

The mechanism of fluid exudation is as yet not completely understood. Its study revolves about the normal formation of lymph, a process which at the present day is not completely explained. Virchow was of the opinion that the passage of fluid into the tissue is in response to a demand for increased nutrition, made by the rapidly multiplying cells. Cellular proliferation, however, appears later than fluid exudation, and the constitution of the fluid should

be essentially the same as that of normal lymph were this assumption true. Two other reasons assigned are, (1) necrosis of the tissues leading to increased hydrogen ion concentration in the tissues and, (2) the slowing of the current inducing a certain amount of asphyxia. Both of these circumstances tend to influence the reaction of the part toward the acid side, and it is well known that the acid protein attracts available water which must come from the blood and lymph. Such an explanation, however, does not account for the large amount of solids in the exudate. Hirschfelder reports that he found no local acidosis in mustard oil conjunctivitis. Rous, however, demonstrated local acidosis in areas of perverted circulation. Ostwald maintained that in inflammation the permeability of the endothelial lining of small blood vessels is increased. It would therefore seem possible that as the fluid passes through the wall in excess, it would carry with it a large amount of the colloids in the plasma. If in normal lymph formation there be a definite secretory activity of the endothelium, then

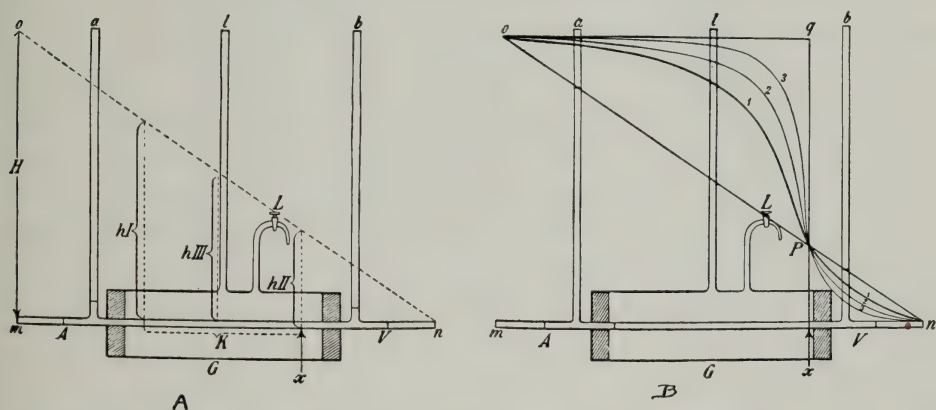


FIG. 59—Diagrams from Klemensiewicz' *Die Entzündung*, to illustrate causes of slowing of current and fluid exudation. A shows normal capillary circulation. The glass cylinder *K* is plugged at each end with rubber stoppers. The tube *m-n* is of glass except within the vessel *K* where it represents a capillary and consists of a piece of rabbit intestine. The uprights *a, i, b*, are glass water manometers, and *L* is an outlet from *K*. A flow of water is established through *m-n* so that at *m* the pressure is up to the point *o*. The fall in pressure follows a diagonal represented by the line *o-n*. Fluid accumulates in the vessel *K* by transudation through the capillary and represents normal tissue pressure when the pressure indicated by *hI, hIII, hII* are attained, and may be maintained by dripping out of *L*, which represents lymphatic drainage.

B shows the changed pressure relations in inflammation, where owing to excessive outflow of fluid from the capillary and inadequate drainage, the fall of pressure, instead of following the line *o-n*, is represented by the curves 1, 2 and 3. This is due to the fact that the increased pressure in *K* compresses the gut part of tube *m-h* at its point of least intravascular pressure, namely at *x*. Thus, pressure is increased in the part toward *m*. As pressure is increased near *m*, there is increased out-pouring of fluid, due to the increased intravascular pressure and this results in increased pressure in *K* which operates more strongly to compress at *x*. Pressure progressively increases in the tube toward *m*, and decreases toward *n*. Thus, circulation is slowed in rate and fluid exudation increases until circulation is stopped by complete compression at *x*.

it is possible that in inflammation the irritation may serve to stimulate secretion. It is also possible that the increased intravascular surface due to vasodilatation, either with or without increased permeability of the capillary walls, may be an important influence in the passage of the fluid. Klemensiewicz offers an explanation based on the studies by Körner of capillary circulation. Normally, the flow of blood through capillaries depends upon a fall in pressure at the venous ends of these vessels, and normally a certain amount of fluid passes through the walls. The transudation of fluid depends upon the intravascular

pressure and the permeability of the walls. If capillary poisons increase the permeability of the walls, the fluid passes out from the points of higher pressure, namely near the arterial ends and may accumulate in the tissues. If the normal drainage paths through the lymphatics and veins be obstructed, as for example by solid exudate in the lymphatics and increased pressure in the veins, the fluid accumulates in the tissues. On a purely physical basis, this may equal the pressure in the arterial ends of the capillaries and thus exceed that of the more compressible venous ends. This may result in compression of the venous ends, higher pressure in the arterial ends and increasing amounts of fluid exudation. Continuance of this vicious circle may ultimately result in the complete compression of the venous end, and final stagnation of the blood in the capillaries. Clotting results and exudation ceases. Recovery may also follow, when the drainage paths become adequate to meet the increased fluid production.

Important purposes are served by the fluid of the exudate. It dilutes soluble poisons and irritants, and thereby reduces their direct effect. Its flow into the lymphatics and venules, although inadequate for the large amount of fluid formed, is in excess of normal, as shown by Samuel, and aids in carrying off the noxious soluble materials. It also provides avenues of escape for the metabolites which are probably formed in excess. Its flow tends toward maintenance of the normal hydrogen ion concentration. Its content of ferments may operate to neutralize toxic bacterial products. The proteolytic enzymes serve to complete the solution of tissues which have been injured or killed, and thus aid in their removal. It is known that the fluid drained from the inflamed part contains digested products of protein, particularly peptone, and the fluid is of increased hydrogen ion concentration. The immune bodies are not increased in concentration, but the increased flow of fluids brings a greater volume of these bodies to the area. The enzymes and immune bodies serve in part to complete the destruction of tissues, and aid materially in combating the growth of, and in destroying, bacteria. The soluble materials so removed pass ultimately into the blood stream, undergo destructive changes in the body, and are excreted through the normal routes of excretion. It is true, however, that the flow of fluid into the lymphatics and ultimately into the blood stream is not always an unmixed good, for by this mechanism living bacteria may be carried to lymph nodes, to remote parts of the body by the blood stream, and be generally distributed, but if the other protective mechanisms of the body be adequate, the danger of this wide dissemination is minimized. If the amount of toxic material absorbed be sufficient, it may irritate the parenchymatous and other organs of the body and lead to alterative or degenerative inflammations. The fluid exudate plays an important part in the formation of fibrin.

Fibrin Formation.—The general phases of this phenomenon have been discussed in the chapter on circulation. The elements concerned in the formation of fibrin, normally present in the plasma, are also found in the fluid of the exudate. This fluid, however, is in an abnormal extravascular position which favors clotting. Constituents provided by the death not only of the tissue cells

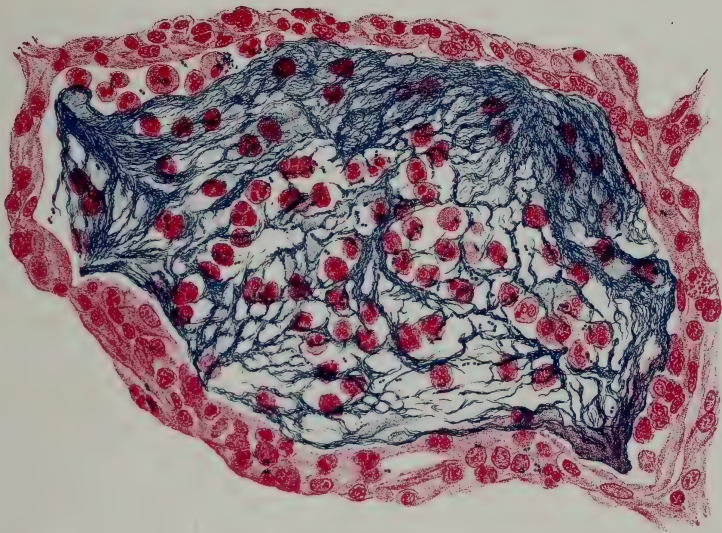


PLATE VI—Fibrin in lobar pneumonia, special stain. Note the strands in the alveolus, with attachment at the spaces of Cohn.

but also of the cells which have migrated from the blood stream, provide the elements of the clot not found in the fluid. Fibrin is likely to be found in the early stage of almost any acute exudate. It is particularly prominent, however, in exudates upon serous surfaces. It may occur as the result of inflammation produced by practically any cause, but is especially likely to be found in inflammation induced by the diphtheria bacillus, by the pneumococcus and related organisms. On the serous surfaces and in pneumonia and diphtheria, the fibrin is likely to persist in the exudate for a considerable time, but in most cases ultimately disappears. Its disappearance, according to Opie, is probably due to proteolytic ferments which originate in the blood and are contained in the fibrin precipitate. If large numbers of leucocytes be present in the exudate and suppuration ensue, or if other destructive elements appear in the exudate, the fibrin is likely to disappear, owing particularly to solution by the proteolytic ferments of the leucocytes and of the fibrin. It may be deposited as a fine network, in heavy bands, or in large hyaline masses. When fibrinous exudates appear upon serous or mucous surfaces, the fibrin is deposited in large part outside the line of the surface cells, but frequently is found to be intimately connected with a fibrin deposit within the superficial tissues. Destruction of the surface cells is not an essential feature in the formation of the fibrin but frequently accompanies it. Further description is to be found in the section on fibrinous inflammation.

Apparently the primary purpose of fibrin formation is to limit the extent of the inflammatory process. Thus, it may form a definite wall of adhesions about a small area in the peritoneum, so as to circumscribe and localize the process. Even within the tissues a similar walling off may be noticed. The fibrin mesh in the lymphatics may serve as a filter, withhold solid material, particularly bacteria, and thus aid in preventing the widespread dissemination of living organisms. If it be not destroyed by proteolytic ferments, its continued presence may serve as a scaffolding upon which the connective tissue growth of the healing process may take place.

Mucin Formation.—Mucin may be found in minute quantities in almost any fluid exudate. It does not appear, however, as the product of exudation but is formed by fixed tissue cells, usually epithelial cells of mucous or other glands, or the glands and surface epithelium of mucous membranes. It is well known that connective tissue may, under certain conditions, form mucoid and

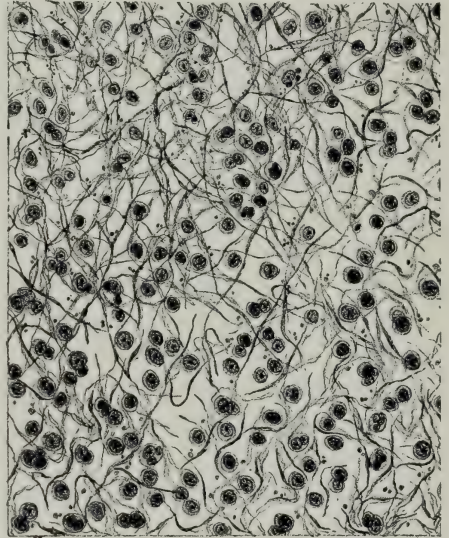


FIG. 62.—Fibrin formation in fibrinous inflammation of pleura; nodal points are apparent. The cells are principally large lymphocytes, since the patient was a victim of lymphatic leucemia.

the endothelial cells may do the same. Mucin is present in larger quantities in acute inflammations of mucous surfaces, the so-called catarrhal inflammation. There is, in such catarrhal exudates, a certain amount of exudation from blood vessels, but the main body of the exudate is the mucin provided by hypersecretion on the part of stimulated epithelial cells, principally glandular. The mucin poured out by these cells, as well as the fluid contributed by the blood vessels, serves the same general purposes as fluid elsewhere, namely, dilution of soluble irritants, maintenance of normal hydrogen ion concentration, and removal of irritants and soluble waste products.

Cells of the Exudate. The Leucocyte.—Unquestionably the most important cell in acute exudation is the polymorphonuclear leucocyte. There are, however, certain types of acute inflammation in which the leucocyte plays only a minor part, as for example, the acute inflammatory, hyperplastic reaction in the lymph nodes in such a disease as typhoid fever. In these instances, exudation is minor as compared with hyperplasia, and when other infections are superimposed and induce exudation, the leucocyte plays the usual prominent part. The mechanism of the participation of the leucocyte concerns especially its passage through the vessel wall, its migration through the tissues and its functions in the exudate. As the blood current slows, the marginal zone contains numerous leucocytes, which adhere to the lining of the vessel, pass through this lining and then wander along lines of least resistance, such as tissue and fascial spaces, toward the point of irritation. They may accumulate in very large numbers so as to form a limiting zone about the focus of injury. The predominant leucocyte is the neutrophile but the eosinophile may take part, and if the patient be the victim of a leucemia the cells of the exudate may include all those which appear in the leucemic blood. In the exudate of lobar pneumonia there are many polymorphonuclear leucocytes, but if, as shown by Winternitz and Hirschfelder, the blood be deprived of most of its granular cells by benzol poisoning, the exudate contains almost no leucocytes. Thus, the cellular content of the exudate is determined to a certain degree by the cellular content of the blood. The leucocyte migrates by virtue of its ameboid movement, a capacity shared, as Jacobsthal has recently demonstrated, by the eosinophile, the myeloblast, and the myelocyte. Maximow demonstrated the ameboid movement of lymphocytes, and the same property is possessed by the plasma cell, the endotheliocyte and the fibroblast. The phenomenon of the ameboid movement is now generally conceded to be due to alterations of surface tension, although other physical properties of the cell and medium are not without considerable importance (Mast). The phenomenon is explained very clearly by Wells as follows:

“Imagine a drop of fluid suspended in water—let it be a drop of protoplasm, or oil, or mercury; the drop owes its tendency to assume a spherical shape to the surface tension, which is pulling the free surface toward the center and acting with the same force on all sides. The result is that the drop is surrounded by what amounts to an elastic, well-stretched membrane, similar to the condition of a thin rubber bag distended with fluid. If at any point in the surface the tension is lessened, while elsewhere it remains the same, of necessity the wall will bulge at this point, the contents will flow into the new space so offered and the rest of the



PLATE VII—Margination of leucocytes in dilated capillary of frog mesentery. The leucocytes are faintly colored cells in the peripheral zone of the current.

wall will contract; hence the drop moves toward the point of lowered surface tension. Conversely, if the tension is increased in one place, the wall at this point will contract with greater force than elsewhere, driving the contents toward the less resistant part of the surface, and the drop will move away from the point of increased tension."

Ameboid movement, as observed in the migration of the leucocytes, depends upon chemical alterations in the tissues and fluids. The reaction to chemical stimuli is referred to as chemotaxis. Chemotaxis may be positive or negative according to whether it attracts or repels the cells. Chemotaxis may be determined by the acidity or alkalinity of the medium, or by the presence of certain more or less definite chemical substances. In the case of ameboid movement in inflammation, it seems likely that various factors are concerned. The injured area is undoubtedly more acid than is the normal plasma. There are numerous by-products of tissue destruction including urea and other extractives. In bacterial inflammation, there are the organisms themselves and their soluble products. Inasmuch as bacterial inflammation is particularly likely to be rich in leucocytes, it is probable that the bacterial products have an important positive chemotactic influence. Certain substances may produce exudates rich in leucocytes, as for example, such vegetable substances as aleuronat and inulin. Turpentine produces exudates containing leucocytes and very rich in fibrin. Chemotaxis is probably not the only factor which operates in the movement of leucocytes. The studies of Wright and his colleagues demonstrate the migration of leucocytes to such inert substances as glass. This cannot be explained by chemotaxis. Wright and Colebrook suggest that stimulus is due to the presence of a solid substance, "the wall of a receptacle, a foreign element introduced into the blood, a meshwork of fibrin, a compacted mass of corpuscles, in short anything upon which the leucocytes can get a prise or hold." The leucocytes probably show no motility in circulating blood because no foothold, so to speak, is provided, but when they take a marginal position, the solid vascular wall offers a foothold. Movement depends upon securing a foothold or prise and occurs without chemotaxis, but certainly in inflammation, chemical attraction is of great importance in determining the direction and mass of leucocyte migration.

Apparently the leucocytes serve two important functions in inflammation. They ingest and remove bacteria, solid particles of cell and tissue debris; they also furnish to the injured area a certain amount of proteolytic ferment which serves to break down injured tissues and thus aid in their removal. Fluid materials are easily removed from the area, and if the cells be broken into fragments they may become more readily the object of phagocytosis than if they be intact. Thus, the leucocyte aids materially in the removal of the debris and in preparation of the area for subsequent repair.

Phagocytosis.—Phagocytosis is the process of ingestion of foreign bodies by a cell. The phagocyte is a cell which ingests foreign bodies. Metchnikoff studied extensively the nutrition of certain of the lower forms of animal and vegetable life and their defenses against invasion of harmful parasites. In this work he was led to the conclusion that the defense of higher animals depends in a great part upon the cellular phenomenon of phagocytosis. It is well known

that the process of phagocytosis involves three steps; first, the approach of the cell to the material to be taken up; second, the ingestion of the material; third, the destruction of such material as may be dissolved by the digestive fluids of the cell. The approach of the cell to the material to be ingested depends, as has been indicated above, upon the phenomenon of chemotaxis. The actual ingestion of the foreign material depends upon the motility of the cell protoplasm. Thus, both the movement of the cell and the ingestion of the particles depend upon a common property of cells, namely, motility, and this as we have stated is probably entirely dependent upon alterations of surface tension. This should not be

taken to mean that other properties of the cell play no part, such as stickiness, internal structure, isotonicity and hydrogen ion concentration of the medium (see Fenn). After the material is within the cell body, it becomes enclosed in a vacuole which contains a fluid poured out by the cell. This fluid contains enzymes, which operate in an acid medium. Naturally, the digestion of the particles depends upon their solubility by the digestive fluids, but if the particle be insoluble it may remain within the cell or be extruded with the wastes of the cell. Much light has been thrown upon the physical basis of phagocytosis by the work of Jennings, who showed that the ameboid activities of cells may be simulated by the use of inert materials such as a drop of oil or metallic mercury. These experiments indicate very clearly the physical character of the activity of

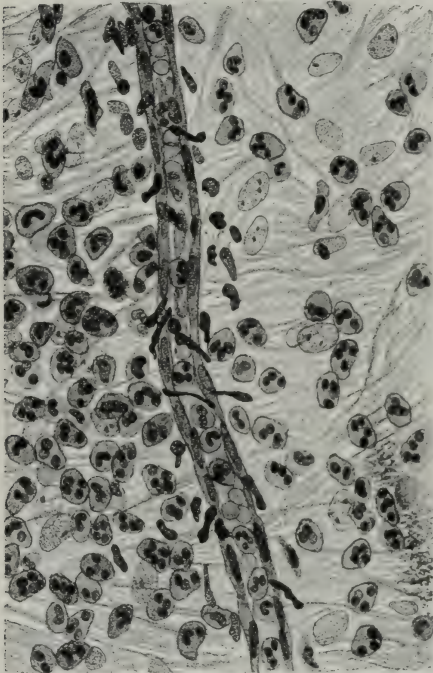


FIG. 63—Emigration of leucocytes through the walls of a minute capillary, and further migration into tissues.

amebæ. The leucocyte, however, differs from the ameba in that it is not a free living organism, that it depends in large part upon the blood for its nutrition and that it will not live outside the body for any length of time; its irritability and movement differ materially from that of the ameba. In the process of inflammation, however, the leucocyte exemplifies phagocytic activity in the highest degree. In addition, phagocytic activity of lesser degree is exhibited by other cells of the blood such as the eosinophile, the myelocyte, the myeloblast, in slighter degree the lymphocyte, and of the fixed tissues the endotheliocyte and probably also connective tissue cells. It is almost certainly true that whatever influences the phagocytic activity of the leucocyte, also dominates the same activity of the other cells. Apparently the most important function of the phagocyte furnished by the blood is the ingestion and destruc-

tion of bacteria, whereas the fixed tissue cells, particularly the endothelial cells, take up and destroy fragments of other cells and tissues. Much the same substances which influence the motility of cells, influence the phagocytic capacity also. As pointed out by Wolf, sterilized and living cultures of bacteria, whether pathogenic or non-pathogenic, the products of protein disintegration such as peptone, amino-acids, as well as carbon dioxide and a large number of crystalloids, may favorably influence phagocytosis. She finds that crystalloids, whether inorganic or organic, may be positively or negatively chemotactic. She has demonstrated that amino-acids and amines are to a certain extent positively chemotactic.

It is well known that the fluids of the body contain, even under normal circumstances, a substance, the opsonin of Wright or the bacteriotropine of

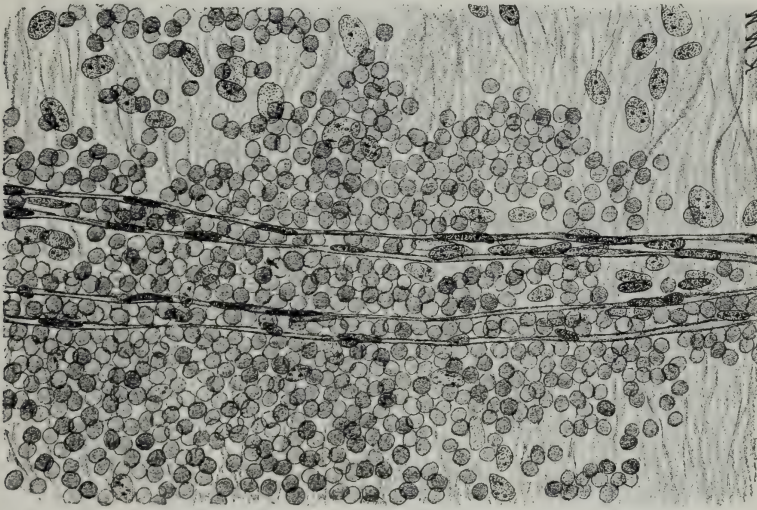


FIG. 64—Hemorrhage in acute inflammation of frog mesentery.

Neufeld, which operates upon the material to be taken up so as to render it more favorable for ingestion. Opsonins act upon bacteria, animal cells and fragments of cells, and perhaps also upon inorganic particles, although this last phenomenon has not been conclusively demonstrated. The content of opsonin in normal blood is relatively low, but it may be materially increased by specific immunization. The activity of normal opsonins may be distinctly increased by the presence of complement, but complement plays a relatively small part in the action of immune opsonins. In any case, the presence of complement is not essential to opsonic activity. Immunization increases the capacity of the organism to combat bacterial infection. It is possible also to immunize animals against heterologous animal cells, so that their defense against the injection of these cells may be increased. Bacteria apparently are taken up more readily if they be dead, but may be taken up alive. In the latter case they are sometimes destroyed within the cells, but on the other hand may continue to multiply within the cell and ultimately lead to its destruction. The migration or

transport of leucocytes, which have ingested living bacteria, is sometimes responsible for the wide dissemination of the organisms throughout the body. As a rule, the normal temperature of the animal from which the phagocytes originated is the optimum. In a general way, it may be stated that the resistance of bacteria to phagocytosis and to opsonization runs parallel to their virulence. Furthermore, this resistance is not lost on the death of the bacteria. Some of these organisms show evidence of their resisting capacity by the formation of capsules; others do not. Whether there are definite alterations of the bacterial membrane, or whether the bacteria form an anti-opsonic or antiphagocytic substance, is not definitely known.

Cells Other than Leucocytes.—*Lymphocytes* appear in the exudate but are

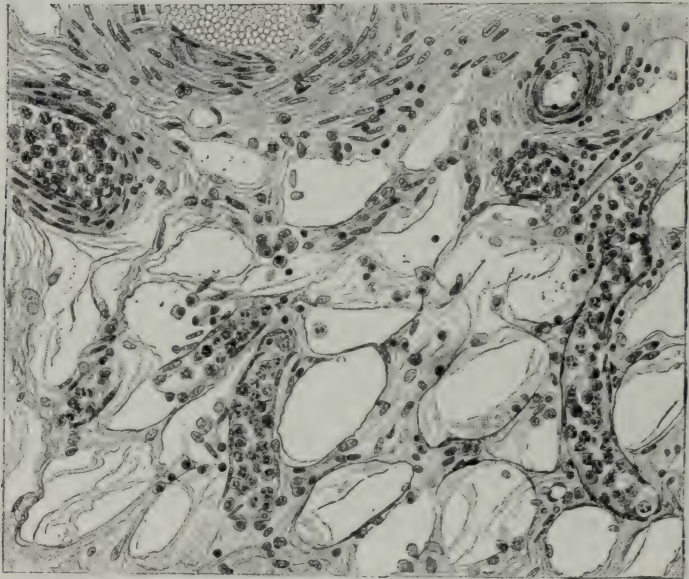


FIG. 65—Masses of leucocytes within capillaries and tissues of vermiform appendix in early suppurative inflammation.

not likely to be numerous in the more acute inflammations. As inflammation becomes subacute and then chronic, lymphocytes may be found in larger numbers. Their ameboid activity is certainly restricted, but is sufficient for them to migrate through vessel walls, as observed by Maximow, Councilman and others. Lymphocytes occur commonly in the tissue spaces and may move from different locations toward the point of injury. By the use of Shridde's modification of the Altmann stain, it is possible to show that hemal lymphocytes contain in the cytoplasm small granules about the size of those in the neutrophils, whereas the histogenous lymphocytes contain fewer but larger granules. Adami maintains that the majority of the lymphocytes in inflammation are histogenous. Their purpose in the exudate is by no means clearly understood. From the work of Opie, it is probable that they are a source of a proteolytic ferment, which he isolated from lymph nodes and which operates in a weakly acid medium. The same acid medium which is likely to occur in necro-

tic and inflammatory areas, favors the action of this enzyme, and at the same time inhibits the activity of anti-enzyme. Jobling and Peterson found that lymphocytes contain a lipase, and it is suggested that the large collection of these cells in the chronic inflammatory areas around tuberculous foci, may serve by the action of the lipase to break down the waxy shell of the bacilli.

Erythrocytes appear in the exudate either by passage through the vascular wall, the process of diapedesis, or they accumulate in large numbers by rupture (rhexis) of the vessel wall with hemorrhage. The latter process is easy to understand, since we know that in inflammation the vessel walls are injured and weakened, and the thin walls are subjected to an increased intravascular pressure. The passage outward of cells by diapedesis, however, is less well understood. It may be a manifestation of minor degrees of rhexis. It was formerly supposed that the red cells pass out through the junction spaces between the endothelial cells, but when it was demonstrated that these spaces probably do not exist in life, that they are filled by a cement substance or cell bridges, this hypothesis was abandoned. Examination of the vessel wall shows no separation through which these cells may have passed. A theory of considerable importance is that the red cells which are colloidal, may pass through the colloidal substance of the endothelial cells without leaving a trace of this passage. As an example of the phenomenon, a drop of mercury placed on the top of a mass of soft gelatin, sinks gradually through the gelatin and leaves no trace of its passage. This explanation presupposes a rather exact balance between the colloidal substances normally and an altered relation in inflammation. Red cells do not pass through the normal endothelial cell in any noticeable degree, but it may be assumed that in inflammation the cytoplasm of the endothelial cells may be so changed as to permit of this curious colloidal phenomenon. There are no facts that tend to indicate a definite purpose on the part of the red cells in the exudate. They carry oxygen, but it is obviously in small amounts, probably not greater than can be provided by diffusion. Both diapedesis and hemorrhage per rhexis must be regarded as purposeless accidents in the course of inflammation.

Platelets are found in small numbers in the inflammatory exudate and may be seen to constitute the centrum of the fibrin asters. They are rarely seen as free bodies, probably because of the rapid clotting of the fluids and the consequent agglutination of the platelets. The mode of passage through the intact vessels is unknown. Their function is unknown except in connection with fibrin formation. A suggestion as to their function may be based on the observations of Levaditi, who found that following the injection of cholera vibrios, they are often found clumped around small masses of platelets. It was subsequently determined that this phenomenon, thigmotropism, is favorably influenced by the presence of opsonins, but its definitive purpose is by no means understood. If bacteria be clumped about a substance and immobilized, phagocytosis may occur more readily. Platelets are deposited quickly on injured endothelium and endocardium, and may thus serve to plug small injuries of the vascular system.

The Endothelial Cell.—There are present in the exudate numbers of large mononuclear cells which have marked phagocytic power. These do not accumulate in great numbers in the early stages of exudation, but appear subsequently in many of the forms of inflammation. They are particularly likely to be found following certain causes of inflammation, namely in reaction to the leprosy bacillus, the tubercle bacillus, the typhoid bacillus and to foreign bodies. They phagocytose tissue debris, dead cells, inert granules of various kinds such as pigment, bacteria, particularly those just mentioned, and red blood cells. By virtue of their motility they then remove these materials from the inflamed area. In brief, they function as scavengers in clearing the inflammatory area so as to permit of subsequent repair, and their action is directed more

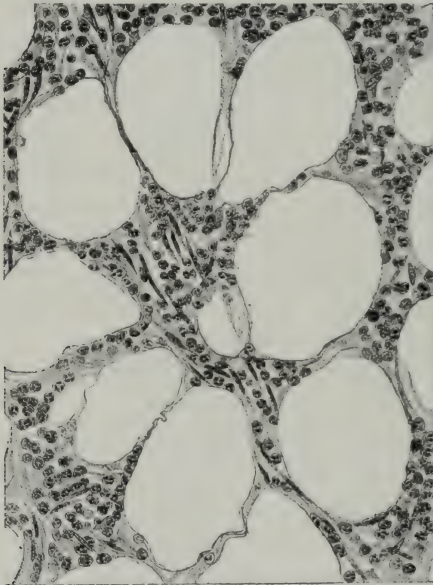


FIG. 66—Leucocytes in tissues in early suppurative inflammation of animal omentum.

especially towards particles of tissue and cell debris than bacteria. The morphology of these cells varies considerably in different exudates and under different conditions, but in all forms the function remains the same. Investigators working very largely on a morphological basis have given a considerable number of names to cells, which, in the hands of numerous students of the subject, are regarded as embryologically and functionally identical. Thus, such names as primitive wandering cell, resting wandering cell, clasmatocyte, polyblast, adventitial cell, pyrrol cell, carmin cell, histiocyte, macrophage, endothelial leucocyte, splenocyte, monocyte, and transitional cell have been applied. The more recent studies of Maximow would indicate that practi-

cally all the cells of the exudate, furnished either from the circulating blood or from the tissues involved, originate from essentially the same primary cells of the mesoderm. How they are subsequently differentiated is a matter of no great moment in this discussion. Inasmuch as these various names for cells appear in the literature, it is well to consider a few of these forms. The primitive wandering cell was described by Saxer and later by Maximow as the small, mononuclear cell of the embryo, which arises from the mesoderm and subsequently by differentiation gives rise to either hematogenous or histogenous wandering cells of the body. The clasmatocyte was described by Ranvier as a cell which in its actively motile state is found to have a large nucleus, and a somewhat granular cytoplasm which divides into numerous processes, and as it passes through the tissue spaces is likely to leave behind small particles of cytoplasm. The polyblast of Maximow is a cell which varies considerably in form but is essentially a large mononuclear with a deeply stained nucleus, some-

times of irregular form, and an abundant cytoplasm which shows no granules. These he considered might originate from migrating lymphocytes, or from preëxisting wandering cells of the tissues which might be directly transformed into polyblasts, or become transformed by passing through a stage in which they resemble clasmotocytes. The adventitial cell described by Marchand, is a small round cell found in the tissue especially in the region of the blood vessels, and in our opinion is probably identical with the small cells described by Councilman as lymphocytes, which appear in the perilymphatic, and probably also perivascular, structures. The pyrrhol cell and the carmin cell are cells which are especially susceptible to vital staining, that is, to staining following injection of dyes into the circulating fluids of the body. The histiocyte is described by Aschoff as a large mononuclear cell, including those which take the vital stain and probably others, but which is of histogenous origin, that is, originates from cells in the tissues. The term macrophage was employed by Metchnikoff to designate phagocytic cells which originate in the tissues. H. M. Evans, however, maintains that these cells are identical with the vitally staining cells. Mallory employs the term endothelial leucocyte to designate the large wandering cell, both of the circulating blood and the tissues, which has notable phagocytic properties. He believes that all these cells originate from vascular endothelium, that they appear in the blood stream following multiplication of the endothelial lining and desquamation of cells, that they migrate in the course of inflammation through the vascular walls and may subsequently multiply in the tissues. Pappenheim uses the term splenocyte to indicate the macrophage of histogenous origin which migrates to the spleen and continues to exist there, possibly, according to Pappenheim, as the local producer of hemolysin. The monocyte is a similar cell appearing in the circulating blood. Both of these he believes to be descendants of those cells which take vital stains. The transitional cell, originally described by Ehrlich as the transition form between the large mononuclear and the polymorphonuclear cells of the blood, is regarded by F. A. Evans as a cell probably originating from the bone marrow and to be grouped, because of its positive oxidase reaction, with the leucocyte series. It is a phagocytic cell which occasionally appears in the tissues in the course of inflammation, but is far outnumbered by the vitally staining histogenous cells which contain no oxidase.

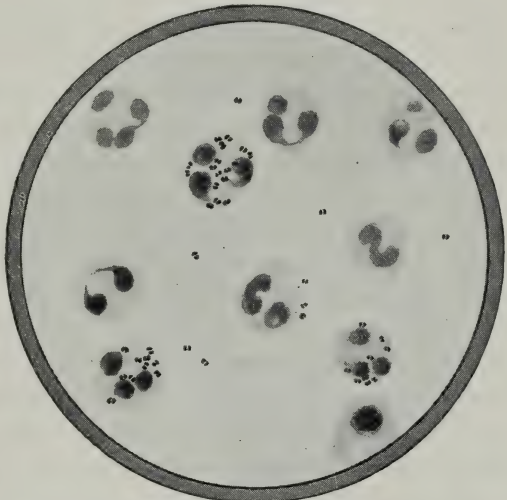


FIG. 67.—Drawing showing phagocytosis of gonococci by leucocytes in urethral exudate.

From the numerous studies of this group of cells, various origins have

been ascribed. It is generally admitted that they have the same embryological origin, but their more immediate derivation is differently interpreted. We may quote F. A. Evans as follows: "From the literature, then, although it is manifestly unfair to interpret the opinions of the more prominent students of the subject along such narrow lines and without further exposition, one may formulate in general the following different hypotheses: that the different types of mononuclear cells of the blood and tissues are (1) lymphoid (Maximow), (2) endothelial (Mallory), (3) histogenous (Tschaschin), (4) in part histogenous and in part hematogenous (Marchand, Aschoff, Pappenheim, Kiyone)." From the more recent investigations of Evans, Downey, McJunkin and Foot, based upon morphological studies of the blood and of tissues, with the use of vital stains and by the aid of phagocytosis of pigment granules, it may be stated very simply that these cells which are identical functionally, probably all originate from endothelium of blood vessels or of the lymphatic spaces. McJunkin is inclined to support Mallory's view that these cells are primarily exuded cells from the blood stream, originally the endothelium of the vessel wall. Foot, however, concludes that they are probably derived in certain part from the proliferating vascular endothelium in the immediate vicinity of the lesion which calls them forth, rather than from the vascular endothelium in general, and that they do not originate either in the omentum or the connective tissue cells or from lymphocytes. For purposes of simplification we may use the term endotheliocyte or endothelial phagocyte, to cover the various forms of the large mononuclear phagocytic cell. From the point of view of function it seems apparent that these cells are a unit. Their functional importance is the same whether they originate entirely from circulating cells in the blood originally derived from vascular endothelium, or in large part are the direct descendants of proliferating vascular endothelium in the inflamed area. Their motility depends upon the same conditions that determine this property of the leucocyte. Their phagocytic activity is influenced undoubtedly by the action of opsonin. This was shown clearly by Hektoen and others and confirmed by Karsner, Amiral and Bock. In low grade inflammations affecting serous surfaces, it is highly probable that some of the mononuclear phagocytes originate in the surface endothelium, as is indicated by the work of Karsner and Swanbeck on the absorption of particulate matter in the pleura. This, however, does not alter the general principle of origin from preëxisting endothelium, either of the vessels or tissues.

The Plasma Cell.—The plasma cell in areas of inflammation was described and named by Unna. It is a small cell slightly larger than the lymphocyte, but sometimes attains almost the size of the endothelial cell. The cytoplasm is non-granular and takes rather faintly, but sometimes deeply, the basic stain. The nucleus is situated eccentrically and is about the size of the nucleus of the lymphocyte. The chromatin is arranged in small masses, often in conical form with the base immediately under the thick, nuclear membrane, and the long axis in radial position, giving rise to the descriptive term "cartwheel" nucleus. The plasma cell may be found in acute inflammatory exudates, but is much

more common in the subacute and subchronic forms of inflammation, where large numbers of such cells may be seen. The origin of these cells has been the subject of considerable controversy. It has been thought, from comparative histological study, that the cell originated from the endothelial cell. Most modern workers, however, are of the opinion that the cell is derived from the lymphocyte. Mallory is so firmly convinced of this that he places the plasma cell as a subvariety of the lymphocyte. Whether this transformation is a property of lymphocytes derived from the blood, or of lymphocytes derived from the tissues, or both, is an open question. Adami is of the opinion that the lymphocyte of inflammation is very largely of histogenous origin and concludes that the plasma cells are almost entirely derived from the histogenous lymphocytes. Plasma cells are slightly motile and have phagocytic powers, apparently more particularly directed toward inert particles than toward bacteria. Aside from this minor function of phagocytosis the importance of the plasma cell in inflammation is unknown.

The Mast Cell.—The mast cell is normally present in the blood stream in very small percentage and is also said to occur within normal tissues. It plays a very small part in the inflammatory reaction and probably is derived very largely from the blood stream, since in inflammation in leucemic patients mast cells may be found in considerable numbers. These are the basophilic leucocytes of the blood, and show a slightly indented or polymorphonuclear nucleus. The cytoplasm is fairly rich and contains granules variable in size and form, which take the basic stain deeply. Such cells are found more commonly in mild subacute and subchronic inflammations than in the acute forms. They are especially prone to degenerative changes so that the nucleus may be very faintly stained, or the cell may be fragmented and its granules distributed about the area. These granules may be mistaken for bacteria and sometimes for minute animal parasites. Certain authorities regard the cells as a degenerative form of the plasma cell or of the endothelial cell. It has slight ameboid movement but apparently plays little part in phagocytosis and has no other known function in inflammation.

The Eosinophile.—This may appear in acute inflammation but is more likely to occur in connection with the subacute or chronic variety. The acute inflammation indicative of a reaction in some forms of hypersusceptibility, may show in the exudate considerable numbers of eosinophiles, as is the case in asthma from hypersusceptibility to particular proteins. It may also be found in considerable numbers in the local reaction to diphtheria toxin. In the case of asthma it is associated with an increase in the number of circulating eosinophiles. It is very likely to be found in the chronic inflammatory reaction in the neighborhood of cancer of the uterus and in inflammatory areas of the intestinal canal, especially in the appendix. Infections by certain animal parasites, particularly the *trichinella spiralis*, are accompanied by an increase of the eosinophiles of the blood. The early stage of the local reaction to *trichinella spiralis* also shows eosinophilia, but this is not constant in local reactions to other animal parasites. The large numbers of these cells in certain chronic

inflammations would indicate that perhaps they originate within the tissues, either from previous existing cells there, or as the derivative of cells which have infiltrated from the blood. The polymorphonuclear eosinophile must be regarded as an adult blood cell, incapable of division, but less mature forms may migrate and divide in situ. According to Liebreich, eosinophiles may be formed in areas of hemorrhage as the result of some peculiar substance formed during the process of coagulation of the blood. According to Jacobsthal, eosinophiles are capable of extruding the granules when they phagocytose objects. He finds that the ground substance of the cytoplasm is a clear, basophilic, homogeneous material. It would appear from his studies, as well as the work of others, that the eosinophile granules are capable of considerable change in number. When the eosinophiles exhibit ameboid movement, the pseudopodia which are projected, contain only the basophilic ground substance. There can be no doubt that the eosinophile is capable of phagocytosis, but any other functions in the inflammatory process are unknown.

Types of Inflammation.—As has been indicated, certain elements of the exudate are likely to predominate in any given inflammation, and the process is designated as serous, fibrinous, purulent, etc., according to the type of reaction. In all the acute exudates, practically all the elements described above play a certain part, and although an exudate may be described as serous, this designation does not exclude the participation of leucocytes, fibrin and other elements. Sometimes it is difficult to determine the predominance of one particular element. If two elements appear to predominate, it is customary to employ combined terms such as serofibrinous, seropurulent, fibrinopurulent, etc., the second part of the term indicating the relative preponderance of the one element over the other. The personal equation often decides the designation of the inflammation in questionable instances. It is of further importance to note that the character of an inflammatory process may change from day to day or even from hour to hour, so that any such designations as indicated here refer to the condition at the moment of observation. Thus a fibrinous pleurisy may in a few hours become a fibrinoserous pleurisy and may subsequently become a purulent pleurisy. A serous meningitis may rapidly become a purulent meningitis and similar changes may be noted in practically any type of inflammation.

Serous Inflammation.—Serous exudates are particularly likely to occur in the early stage of inflammation of serous cavities, and in inflammations elsewhere produced by mild irritants. In the tissues, such inflammations usually are in response to mild irritation, and may appear in the deeper reactions to corrosive or chemical poisons upon the skin or other surfaces. The common experiment of painting the rabbit's ear on the inner surface with croton oil, shows in the earlier stages of the reaction a marked serous exudation. Cells are present in small numbers and fibrin is formed in small amounts. In this instance, however, as the exudation proceeds, the cellular elements play a much larger part. Blisters which form on the skin, as the result of irritation, contain principally serum, with little fibrin and only a few cells, but, as is well

known, the character of the material of the blisters may change so that they become pustules. In the serous cavities of man or of animals, irritation, either chemical or bacterial, may give rise to extensive serous exudate. The amount of fluid accumulated in the peritoneum may exceed several liters and in the pleura may be a liter or more. Even in the pericardium a liter of fluid is occasionally found. Invariably, however, a certain amount of fibrin is deposited on the surface, and in the histological examination of such a membrane, the inflammation may be designated as fibrinous if no knowledge be possessed of the general condition of the cavity. Such fluids are of high specific gravity, contain considerable quantities of protein, and upon microscopic examination show desquamated endothelium and large numbers of leucocytes. When removed, such fluids are likely to clot in the containers. If clotting has occurred in situ, further clotting is not likely to occur upon removal.

Fibrinous Inflammation.

—This is well exemplified in the local reaction to diphtheria. The implantation of the diphtheria bacilli in the tonsil leads first to redness, swelling and tenderness or pain in the tonsil and rapidly to the formation of the fibrinous exudate. This appears upon the surface as a white or pale yellow, smooth mass, sharply defined and of semisolid consistency. Subsequently, it shows roughen-

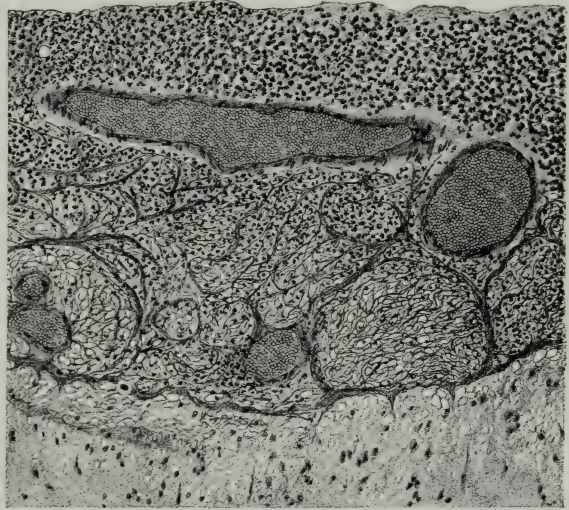


FIG. 68—Acute fibrinopurulent inflammation of meninges. Note the dilated vessels.

ing of the surface due to solution of the fibrin, and may become yellow in color due to an increased number of leucocytes. When examined microscopically, it is found to be made up of a network of fibrin strands, arranged very irregularly in the form of small hyaline bands or masses and a fine network of intercommunicating fibrils. The fibrin is found also in the surface epithelium and sometimes beneath the basement membrane in the substance of the tonsil. The same general principle is applied to fibrinous diphtheritic exudate anywhere. Fibrin formation is also well exemplified in lobar pneumonia. Fibrin may be formed in numerous other parts of the body and various terms have been applied. The term diphtheritic inflammation is now restricted to that form produced by the diphtheria bacillus. Exudates similar in gross and microscopical character appear also in the intestinal canal, particularly in the small intestine in various forms of enteritis and in the large intestine as a result of infection with the dysentery bacillus. Although the term diphtheritic was formerly applied to these inflammations, it has now been

abandoned, and although some apply the term diphtheroid it seems preferable to refer to these simply as fibrinous exudates or fibrinous inflammations of the gut. The term "croupous" inflammation was designed to apply to fibrinous inflammation affecting the respiratory tract below the level of and including the larynx. This is preserved in the term "croupous" pneumonia which is now used synonymously with lobar pneumonia. Inflammations of the serous surfaces are almost constantly accompanied by the formation of a considerable amount of fibrin. In the early stages the fibrin is deposited in the form of a soft, pale yellow or white substance, which adheres to the serous surface very much as butter adheres to bread, when two pieces are buttered and subsequently pulled apart. The old term "bread and butter" pericardium or pleura or peritoneum is still sometimes applied to these early fibrinous inflammations of serous surfaces, with their dull, light yellow, slightly roughened surface. As the fibrin continues to be formed, however, the movement of these membranes may whip the fibrin into more or less heavy bands. Thus, in the pericardium, the whipping action of the heart may form heavy, stringy masses of fibrin which gives the designation "shaggy" or villous heart. The microscopic examination of fibrin is of considerable importance. It may be observed beautifully in certain stages of inflammation of the rabbit's ear. Sometimes, however, the diagnosis is so difficult that special stains specific for fibrin are required. Fibrin takes the acid stain and appears in heavy hyaline masses, hyaline bands, or in fine fibrils. Confusion may be experienced in the differentiation between fibrin fibrils and the fibrils of connective tissue. It must be remembered that fibrin is precipitated out of solution and that, as mentioned in the discussion of circulation, it is to be regarded as a fluid crystallization. Therefore, junction points of the fibrils show larger accumulation with the formation of the so-called "nodal points." These are not found in connective tissue fibrils. In favorable instances it is also possible to demonstrate the fibrin asters or stars. These show as a centrum a collection of platelets or leucocytes, radiating from which are the wavy fibrils of fibrin constituting the aster. Intermingled with the fibrin are always to be found some fluid precipitate in granular form and some of the cells of the exudate.

Hemorrhagic Inflammation.—An inflammation is designated as hemorrhagic when the number of red blood corpuscles is so great in the exudate that the bloody character is apparent to the naked eye, or it may be diagnosed microscopically when the number of red blood corpuscles is obviously excessive. The hemorrhage in the exudate depends partly upon the conditions and severity of reaction in the tissues. Organisms which ordinarily produce suppurative or other types of inflammation may be so extremely virulent as to produce marked lesions of the vessel walls and consequent hemorrhage. The condition of the blood vessels sometimes plays a part; for example, in arteriosclerosis and in chronic nephritis, the smaller blood vessels may be the seat of disease which renders them unduly fragile. The invasion of areas by malignant tumors may also affect the blood vessels, so that either from direct invasion by the tumor or because of a localized weakening of blood vessels in the neighborhood,

an associated inflammation may be hemorrhagic. The condition of the blood is also of importance; for example, in leucemia and in profound anemias whether primary or secondary, there is a general disposition to hemorrhage, and if inflammation occur the exudate may be hemorrhagic. Passive hyperemia in certain areas may also aid in the production of a hemorrhagic exudate. In cirrhosis of the liver there is likely to be hyperemia of the portal circulation, and if a peritonitis or some other local inflammation occur in this area, hemorrhage may complicate the exudate. Certain bacteria are particularly violent in their action on the blood, as for example, the streptococcus hemolyticus, and infections of this sort are not infrequently hemorrhagic. Diphtheria is sometimes so severe as to lead to hemorrhagic tendency and the local lesion may then be hemorrhagic. Anthrax commonly produces hemorrhagic inflammation. The destruction of blood vessels by liberated ferments may alter the inflammation so that it is hemorrhagic, as for instance in the so-called acute hemorrhagic pancreatitis. Bacteria operating in certain situations, may show a tendency to hemorrhagic disease. The notable example of this is tuberculosis affecting the pericardium and other serous cavities. The permeability of vessels in early infancy is commonly greater than in later life. Hence, inflammations in early life are more frequently hemorrhagic in character. Under certain conditions, probably increase in virulence as a most important one, diseases of unknown cause may show hemorrhagic tendencies. Under ordinary circumstances the local lesions of measles and scarlet fever are mild inflammatory reactions, but may sometimes, when the disease is very severe, be distinctly hemorrhagic. The lesion of smallpox is, as a rule, first serous and then suppurative, but in occasional severe cases the exudate may be hemorrhagic. It will thus be seen that the presence of a hemorrhagic exudate is in not indicative of a particular cause.

Suppurative Inflammation.—The mere presence of large numbers of leucocytes in the exudate is not necessarily an indication of suppuration. An inflammation is truly suppurative only when it is accompanied by the formation of pus. In the stage of gray hepatization of lobar pneumonia, the exudate in the alveoli of the lung is principally leucocytic in character, but pus in the true sense of the word is not formed. In the instances where leucocytes predominate but pus is not formed, it is preferable to designate the inflammation as leucocytic. With very few exceptions, however, the presence of large numbers of leucocytes is sufficient for the diagnosis of suppuration. Pus is a semifluid yellow or greenish-yellow material, opaque, creamy, and more or less granular. The color is sometimes determined by the organism which produces the inflammation. Thus, the ordinary pyogenic bacteria produce light yellow pus. The bacillus pyocyaneus, on the other hand, produces green pus. The odor, as a rule, is only mildly foul but if gas forming organisms be associated, as for example colon bacillus, the odor may be offensive. The consistency of the pus depends upon how far autolysis has proceeded. In man, suppurative inflammation is almost invariably caused by bacteria but, as in smallpox, an unknown virus may produce the condition. In experimental work suppuration

may be produced by certain chemicals and other substances. The injection of turpentine, aleuronat or inulin into serous cavities produces suppuration. The late stages of serofibrinous or other inflammations of serous cavities, and of croton oil inflammation of the rabbit's ear may sometimes be distinctly suppurative.

The microscopic appearance of the suppurative area shows usually a great predominance of leucocytes, sometimes a moderate amount of serum, but only in the early stages is fibrin present. In the later stages the exudate is made up almost entirely of leucocytes with a few lymphocytes and endothelial cells. The

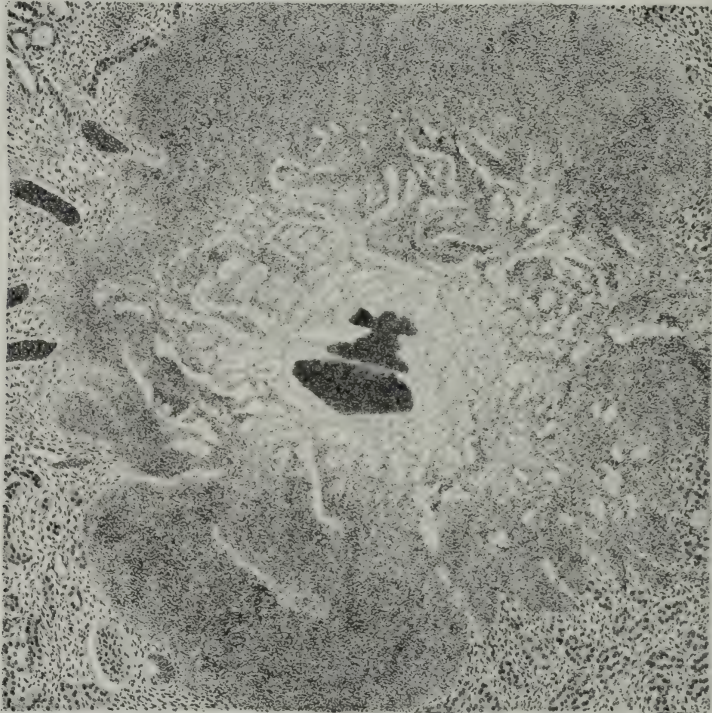


Fig. 69—Experimental embolic staphylococcus abscess in kidney of rabbit. Note the mass of bacteria in the center surrounded by completely necrotic tissue, and this in turn by a mass of exuded cells.

pus cell is the leucocyte in which certain secondary changes have occurred. Cloudy swelling is not uncommon; the cells are usually rich in glycogen; not infrequently fat is present in considerable amounts. Necrosis of the neighboring tissues is usually prominent.

It is possible to distinguish three main forms of suppurative inflammation, namely that upon surfaces, the abscess, and the phlegmon. Inflammation of the skin and mucous surfaces may become suppurative in character, thus changing the simple catarrhal inflammation into a suppurative inflammation. In the common cold, the earlier stages show a serous inflammation, then a thick sticky, mucinous exudate, and in a later stage a thick, yellow mucopurulent exudate whose color is due to a rich infiltration of leucocytes; if the condition

progress further, discharge of actual pus from the nose may occur. The *abscess* is a localized collection of pus. The *phlegmon* is a collection of pus spread through tissue spaces usually parallel with a body surface. An example of the phlegmon is seen in suppurative inflammation of the floor of the mouth, which sometimes starts as a small abscess and then extends so as to involve the entire floor of the mouth, the so-called Ludwig's angina. "Cellulitis" of the subcutaneous tissues is not infrequently a phlegmon. As an example, a suppurative inflammation may be established in part of the thigh; extending deeply it may progress along the lines of the great fascias of the thigh so as to produce an extensive flat area of suppuration.

The abscess is probably the most common manifestation of suppuration. The typical picture of the acute abscess grossly is that of a swollen area, with all the cardinal signs of inflammation, which on palpation gives a sense of fluid material underneath, called fluctuation. If the abscess has extended near the surface, a yellow or greenish-yellow area in the center indicates the presence of pus. The typical picture of the abscess microscopically is that of a generally circular area, in the center of which are bacteria, surrounded by necrotic material, and this in turn surrounded by a wall of leucocytes, centrally degenerate and peripherally healthy. Intermingled with the leucocytes are likely to be found lymphocytes and endothelial cells. Around this the usual vascular dilatation and prominence of capillaries is found, and still further out the beginning of the process of repair and the forming of new capillaries and fibroblasts. As has been mentioned above, the abscess or any other form of suppuration in man is likely to be of bacterial origin. Small abscesses are very common on the skin surface as the result of implantation of bacteria, usually in the hair follicles or as the result of small abrasions. These small abscesses are referred to as boils or furuncles; the condition may be extensive and prolonged and give rise to furunculosis. In certain areas where the skin is thick and there are large columns of subcutaneous fat connecting the skin with more deeply placed fat, carbuncles occur. The carbuncle is an extensive area of suppuration, usually of rather long duration, affecting the subcutaneous fat and communicating with the surface through fat columns which run at right angles to the skin surface. Thus, the carbuncle may have several points of discharge. Microscopically, the carbuncle differs from the abscess in that there are more lymphocytes and endothelial cells, indicative of its longer course. Necrosis and pus formation are present. Careful examination will show the extension toward the surface along the fat columns. In addition to these superficial foci, abscesses may be found in practically any situation in the body including brain, bone and all the viscera. An abscess of any considerable size is to be regarded as a serious manifestation of inflammation, and may be accompanied by secondary inflammation of great importance. Thus, abscess of the hand may lead to an inflammation of the lymphatics which drain this area, and this in turn may lead to inflammation of the lymph nodes. Such inflammation of the lymphatics may subsequently become suppurative in character. The veins draining the part may also become the seat of inflamma-

tion, which may subsequently become suppurative leading to the establishment of a suppurative thrombophlebitis. Either as the result of this thrombophlebitis or by more direct entrance into the blood stream, bacteria may be carried to remote parts. General resistance may be so great that bacteria are quickly destroyed in the blood stream and tissues, or resistance may be so low that the bacteria persist and multiply in the circulating blood, a condition known as septicemia. As a result of septicemia, the organisms may set up inflammation in numerous situations. Thrombi may develop on the heart valves as the result of lodgment of bacteria, producing acute endocarditis. The bacteria may continue to proliferate in the thrombus and the lesion thus

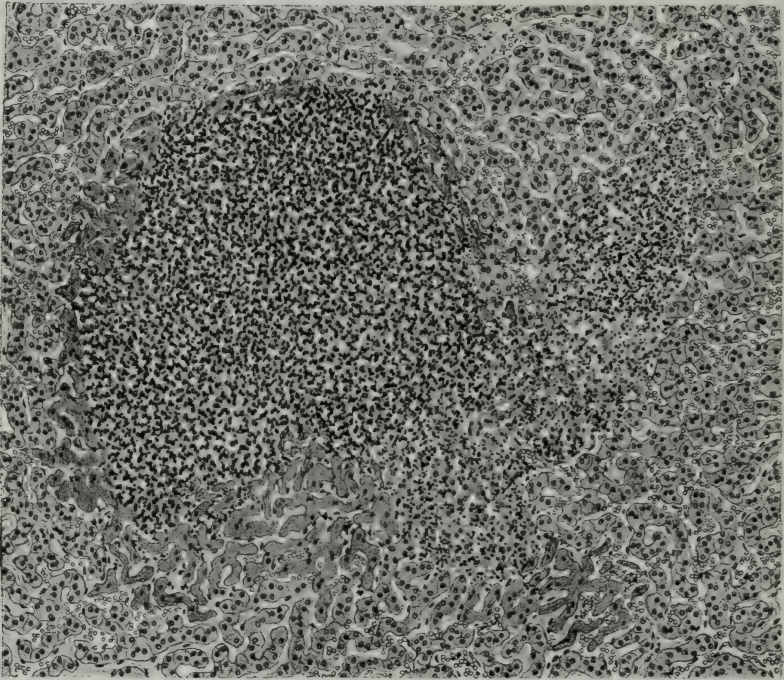


Fig. 70—Abscess of human liver. Note the mass of leucocytes, which has replaced necrotic liver substance.

be a reservoir for further supply of organisms to the blood stream. The lodging of fragments of thrombi from heart valves, or from a suppurative thrombophlebitis, or even the lodgment of small clumps of bacteria, may lead to secondary abscesses in numerous organs of the body, such as the lung, heart, kidney and other situations. The whole chain of events may be represented somewhat as follows: The presence of the abscess may lead to a condition in which there is primarily simply absorption of toxic products, a toxemia. If bacteria gain entrance to the blood stream their presence associated with the toxemia constitutes a septicemia. If to this be added the formation of multiple abscesses, the condition becomes a pyemia. Such a sequence of events may follow any suppurative infection from a minute furuncle to the most severely infected wound.

The progress of the abscess locally is variable. If the infection be rapidly suppressed, the dissolved material is removed by absorption and the solid debris is removed by leucocytes and endotheliocytes. Granulation tissue fills the defect and the area is cicatrized. If the infection persist, the abscess may extend and enlarge. Its extension is along lines of least resistance and if confined by heavy fascias, a phlegmon may develop, as exemplified in the palmar abscess, or cellulitis of various parts. "Pointing" of the abscess means approximation to a surface. Subsequently, the abscess may rupture on to the surface. Abscesses may point on the skin, mucous or serous surfaces, depending upon their location. The pus is discharged through the opening and carries off numerous bacteria and soluble irritants. Thus, the combat against the infection and the process of healing are favored. What is essentially an ulcer is formed. This fills with granulation tissue and finally cicatrizes. If the abscess be deep-seated, the route to the surface is called a sinus.

Parenchymatous Inflammation.—

This term is essentially synonymous with alterative inflammation as used by some schools, or with degenerative inflammation as used by others. Marchand prefers to call it "inflammatory disease" and defines it as composed, on the one hand, of the degenerative sequences of an injurious etiological agent, the acute and chronic reactive processes in the vessels and tissues, the proliferative and reparative tissue changes, and on the other hand, of secondary functional and morphological disturbances. Thus, cloudy swelling,

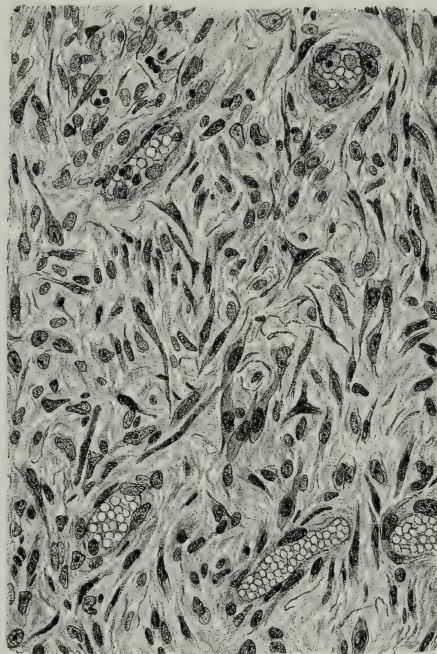


FIG. 71—Young connective tissue (fibroblasts) in early experimental granulation in tongue.

ing, fatty degeneration, hyaline necrosis or other degenerative process may be present. In establishing the identity of the process as an inflammation, it is necessary to have associated with the degenerative changes either exudation or cellular proliferation. Such types of acute inflammation may occur in the heart, liver, brain, spinal cord, and particularly in the kidney. They are caused by circulating poisons of exogenous or endogenous origin, particularly those of infectious diseases, or may be the result of lodgment in situ of bacteria, particularly those of relatively low virulence. Rosenow has emphasized the selective affinity of parenchymatous tissues, as well as other tissues, for special strains of the green-producing streptococcus, and Baehr and his coworkers point out the significance of bacterial infection in reference to certain types of inflammation in the kidney. Neverthe-

less, it seems true that most inflammations of degenerative or parenchymatous type occur as the result of circulating toxic substances. Those introduced from without include such drugs as cantharides, mercuric chloride, arsenic, phosphorus, lead and other poisons. Those produced within the body include particularly the poisonous substances of bacterial infection, as well also as certain poisons probably produced in the body by faulty metabolism. It is important to keep in mind the exact interpretation of the term degeneration, as discussed in the chapter on that subject. There has been great discussion as to what type of degenerative changes, associated with other tissue changes, should properly be classified as inflammation and what should be looked upon as purely degenerative processes. This controversy arises particularly in reference to acute and chronic diseases of the kidney. Simple cloudy swelling of the kidney may lead to much the same clinical phenomena as does mild acute nephritis, but in the former the changes are likely to be of less severity and of shorter duration than in the latter. This, however, is not a satisfactory mode of pathological differentiation. So much doubt exists as to the truly inflammatory character of the parenchymatous inflammations of the kidney, that the term nephropathy has been suggested and is frequently employed in literature. If, however, a distinction between simple degeneration and degenerative inflammation be based upon microscopic indications of exudation or proliferation, it is possible to differentiate the vast majority of cases, although a few instances arise in which the differentiation is difficult and depends upon the personal equation. All forms of acute nephritis show degeneration of the parenchyma, but in addition there are changes which vary from slight proliferation of endothelium of the capillary tufts, to the most marked exudation and proliferation. In some forms of the disease there may be marked infiltration of lymphocytes, plasma cells and endotheliocytes. In other forms there is exudation of polymorphonuclear leucocytes and fibrin formation. The finer shading between those forms with only proliferation of the endothelium of the tufts as the indication of inflammation, those with interstitial proliferation and exudation, and those with actual exudation of leucocytes and fibrin formation, is so gradual that no sharp line can be drawn. Therefore, in our opinion it is quite justifiable to regard all these changes as indications of alterative, degenerative or parenchymatous inflammation.

In the heart, degeneration of the muscle may appear without any associated change in other parts of the tissue, or may be accompanied by infiltration of lymphocytes, endotheliocytes, and plasma cells. In the more severe cases actual invasion of leucocytes is noted. The muscle may show cloudy swelling and fatty degeneration, hyaline necrosis or other severe degenerative manifestations. Similar inflammations of the liver occur but are by no means common. In infectious diseases, the brain and spinal cord may show degeneration of the ganglion cells, nerve fibers and of the myelin sheath, accompanied by severe neurological manifestations, but showing pathologically little exudation or proliferation. In order to designate this as an inflammatory process, however, it is necessary to find either exudation or proliferation. Proliferation is common-

ly observed in multiplication of glia cells and fibers. Catarrhal inflammation may also be regarded as essentially degenerative in type, for it shows degeneration of the parenchymatous cells, that is, the epithelial cells, usually mucinous in type, associated in many instances with only moderate infiltration of leucocytes and lymphocytes. Inasmuch, however, as the hypersecretion of the cells and the outpouring of fluid from the vessels are prominent, it seems justifiable to place catarrhal inflammation in a category subordinate to the general group of alterative inflammations.

In contrast to the parenchymatous inflammations, the same organs may show interstitial inflammatory disease of much the same nature, but the interstitial changes predominate. They may be more specifically referred to as non-exudative interstitial inflammations. Exudates appear in interstitial tissues and the process academically may be regarded as an interstitial inflammation, but both acute and chronic diseases of parenchymatous viscera may occur in which exudation plays little part; the tissues may show infiltration and multiplication of lymphocytes, plasma cells and endotheliocytes which do not appear to be exudative in origin, or the interstitial connective tissue may be notably hyperplastic. The accompanying degenerative changes may be slight. Thus, the inflammatory disease of the viscus, although diffuse, may affect more particularly either the special parenchymatous cells or the interstitial tissues, and the condition is designated as parenchymatous or interstitial depending upon the predominance of the one change over the other.

Catarrhal Inflammation.—This type may appear upon any mucous surface. The exudate is contributed by the mucous cells and by the blood vessels. It varies from a thin, watery secretion with very little mucin to a secretion which may be so rich in mucin as to be semisolid. The material may be colorless or slightly gray, or if there be a mixture of leucocytes, pale or deep yellow, depending upon their number and condition. Microscopically, such exudates show mucin, a small amount of protein, as well as leucocytes, lymphocytes and desquamated epithelial cells in variable numbers. Examination of a mucous membrane, the seat of this condition, shows it to be red, swollen, irritable and tender, and with increased temperature. The disturbance of function is exhibited in the hypersecretion. Histologically, the surface epithelium is the seat of cloudy swelling, sometimes associated with mucinous degeneration of the cells. Desquamation of the cells, either singly or in groups, is common. The deeper cells, particularly those of the glands, are likely to show advanced mucinous degeneration. The tunica propria and submucosa show hyperemia and prominent capillaries. There is usually an infiltration of cells from the tissues and blood, composed in the milder cases principally of lymphocytes and endotheliocytes with a small number of leucocytes. These cells appear not only in the position mentioned but may also be found infiltrating between the epithelium. In the more severe cases, or later in the course of the reaction, leucocytes are found in greater numbers and the exudate may finally become purulent in type. The causes of catarrhal inflammation are numerous and have given rise to much discussion, particularly in that form known as the common

cold. *Micrococcus catarrhalis*, constantly present in the nose increases in number in colds but no convincing evidence is submitted as to its causal relation. *Bacillus influenzae*, *streptococcus hemolyticus* and *viridans*, *pneumococcus*, *bacillus rhinitis* have all been described as causative agents. Foster has confirmed and extended Kruse's demonstration that a filtrable virus may be a cause. Catarrhs may also be caused by irritant gases and by dusts, and it is possible that constitutional conditions predispose. In the genito-urinary tract, gonococcus is an important cause of acute and chronic catarrhs, which in the florid stage are purulent. Catarrhs of the intestinal tract may be caused by many types of bacteria, both saprophytic and parasitic, aerobic and anaerobic; irritation from spoiled foods, irritant or caustic liquids, solid foreign bodies may excite intestinal catarrh.

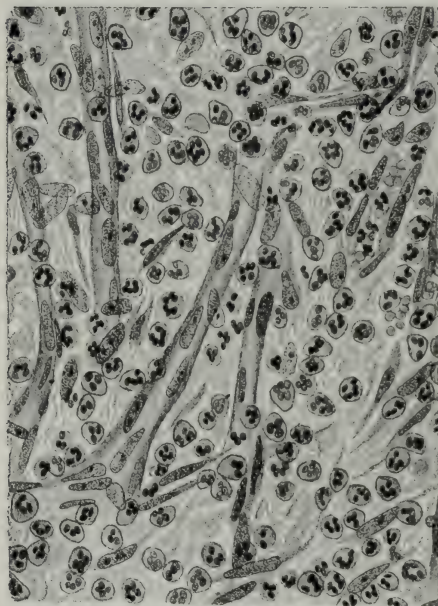


Fig. 72—Newly formed capillaries in infected wound.

Repair.—Almost as soon as the inflammatory reaction becomes evident, the processes leading toward repair begin. Although described in series in this discussion of inflammation, it is of the utmost importance to consider all the processes as going on hand in hand. In inflammations of serous membranes, it is common to observe repair beginning within a very few hours after infection or injury. The same is true of inflammation of other parts. Repair represents the reaction of the fixed tissues to the injury, and in our interpretation constitutes a most important part of the inflammatory process. Perfect restoration of inflamed tissue rarely occurs. A notable exception, however, is the complete healing of the lung after lobar and certain other pneumonias.

Ferments dissolve the exudate in the alveoli and it is removed by expectoration, absorption and phagocytosis, the process of resolution. It is probable that the interstitial tissues are not injured in this type of inflammation, and hence according to certain authorities no stimulus is furnished for granulation. On the other hand, if the ferments fail to dissolve the exudate in the alveoli, it remains as a foreign body and undergoes organizing changes which will be described as the sequence of inflammations elsewhere. For the sake of simplicity, repair may be said to take place in three stages which are more or less intermingled, namely, granulation, organization, and cicatrization. Regeneration of other structures in the destroyed areas is also found during connective tissue repair, but is a variable phenomenon, sometimes of importance, sometimes entirely in abeyance. The primary and simple changes in repair are seen in proliferation of connective tissue and multiplication of blood vessels. This depends practi-

cally entirely upon mitotic division of connective tissue cells and of vascular endothelium. The origin of the new connective tissue cells, or fibroblasts, has been the subject of considerable dispute. Whether these cells originate from old connective tissue which has reached adult stage with condensed nuclei and rich fibrillar structure, whether it originates from the so-called cells of the bundles, small cells resembling lymphocytes found normally in masses of connective tissue, whether it is derived from cells of the exudate such as the endotheliocyte, has been discussed and no adequate conclusion reached. It is possible that the cells of the bundles, and the endotheliocytes may play a part, but from our own observation we incline to the view that the fibroblasts are formed by an active proliferation of the original connective tissue. There is no doubt that in the course of multiplication, the fibroblast may show a stage in which it is practically indistinguishable from the endotheliocyte. In this stage the cell is oval, has young cytoplasm which takes the basic stain lightly, and shows a fairly large, distinctly vesicular nucleus, oval or spherical in form. Subsequently the cell elongates and takes on the spindle form, which in later stages may show cytoplasmic processes and become almost stellate in outline. All the factors that cause fibroblast proliferation are not known, but Carrel has shown that their multiplication is stimulated by a secretion from the leucocytes.

At about the time of appearance of the fibroblasts, examination of the capillaries shows mitotic figures in some of the endothelial cells. Such cells appear larger than their fellows and may project into the capillary lumen. Multiplication proceeds, so that buds composed of new cells project into the tissues. The buds become longer sprouts, and are then hollowed out to form small capillary projections containing blood. These communicate with other sprouts to form new capillary loops. Some authorities maintain that the blood does not enter until adjoining sprouts communicate to provide for circulation. The mass of fibroblasts and new capillaries is referred to as granulation tissue, because when seen grossly at the base of an ulcer, or in an evacuated abscess cavity, the surface is roughened by the projection of soft red granules, one or two millimeters in diameter. These granules contain fibroblasts and new capillaries. In the unopened abscess, microscopic examination shows the granulation tissue outside the wall of leucocytes. In more diffuse inflammations the granulation is more irregularly distributed. Inflammations of serous surfaces



Fig. 73—Reconstruction drawing of newly formed capillary loops in granulation tissue.

show the granulation beginning in the subserous tissues and growing into the exudate. In experimental inflammations, granulation may be found within a few hours after injury.

The granulations may grow into and fill up areas of necrosis or may extend into surface exudates so as to replace tissues or exudate. This process is referred to as organization. The latter term is often employed to include both the granulation and the filling of defects or substitution for exudates. In the case of fibrinous exudates, the line of growing fibroblasts and capillaries may follow the meshes of the fibrin net. This is well seen in organization of fibrinous exudates on serous surfaces, and is particularly well exemplified in the

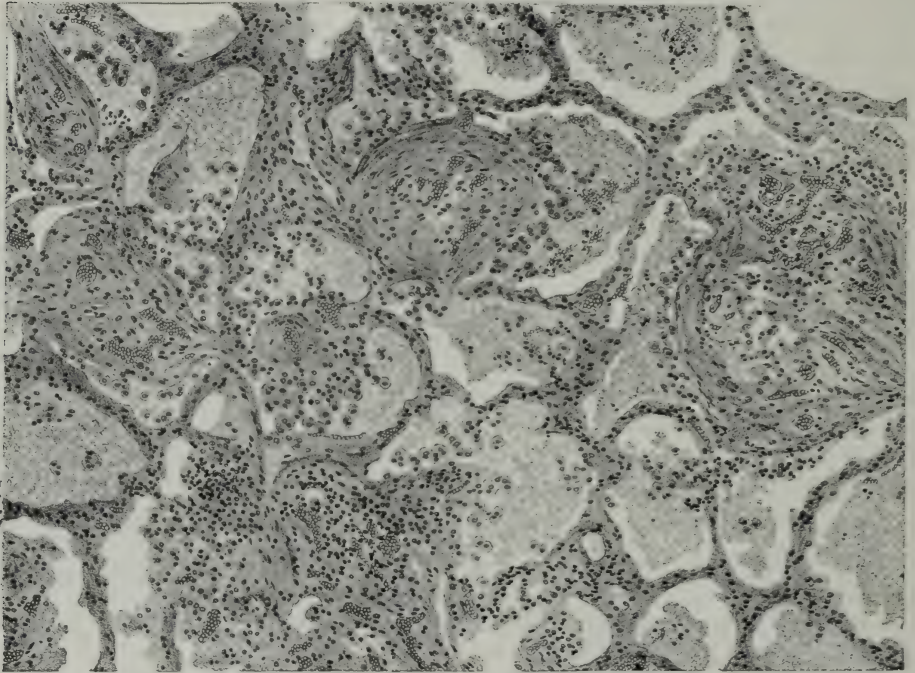


FIG. 74—Organizing pneumonia, showing the growth of new connective tissue following the lines of fibrin.

organization of the alveolar exudate of pneumonia in those cases where solution of the exudate does not occur. The growth of the new cells along lines of fibrin may be an evidence of the phenomenon exhibited by leucocytes when they adhere to some inert solid substance, such as a sheet of glass.

When the defect is filled or the exudate organized, the final stages of repair are noted. The capillaries decrease in size and for the most part undergo gradual atrophy until they disappear. At the same time, the connective tissue shows shrinkage and condensation of the nuclei and the cytoplasm becomes more and more fibrillar, until the whole mass assumes the character of adult connective tissue with its numerous fibrils and sparsely scattered, dense, spindle form nuclei. This transformation is cicatrization and the product is the cicatrix or scar. One of the great problems of biology is the limitation of cell growth

to the structural and functional needs of the body. We may consider that with destruction or removal of the irritant, the stimulus for cell proliferation ceases to act, and that as cell multiplication is discontinued the tissue takes on the adult characters. This explanation does not entirely harmonize with the preceding one, since in certain ulcers where irritation is continued there may be a dense scar about the base. Until the real reason for the balance of cell growth is understood, scar formation will be a problem. By studies *in vitro*, Fischer has shown that the most favorable reaction for growth of the fibroblasts is a hydrogen ion concentration of pH 7.4 to 7.8, of the body, and that either higher alkalinity or higher acidity depresses growth. Thus, the acidity of the inflammatory area cannot be regarded as a stimulus to granulation. Carrell has found that complete aseptic protection of a wound markedly delays cicatrization, but that the application of an irritant such as turpentine, or slight infection such as ordinarily occurs, hastens healing. Apparently irritation in physical or chemical form, serves to hasten healing in spite of any slight alteration in the reaction of the surrounding medium. The careful studies of Carrell, DuNoüy, and their collaborators have added much to our knowledge of cicatrization of wounds. DuNoüy has been able to derive an exponential formula for the rate of healing of surface wounds, which, in practice, serves to prophesy with much accuracy the time required for healing. He points out that epithelialization accelerates the rate of healing and that contraction begins before healing is complete. The disappearance of capillaries is considered by some to be due to pressure by the contraction of the connective tissue, but it is not uncommon to find a scar pallid before it contracts. Undoubtedly, the purpose of the rich vascularization in organization is to provide nutrition for the rapidly multiplying cells. When multiplication stops, the need for the capillaries no longer exists, and their atrophy may be a manifestation of adaptation to the changed



Fig. 75—Organization of acute fibrinous pericarditis. The new granulation has grown from the myocardial margin of the picture so as partly to replace the exudate, some of which in the form of fibrin and leucocytes remain distal to the myocardium.

conditions. It may be regarded as an atrophy of disuse, predisposed to by an assumed collapse of the capillaries when the physico-chemical state of the tissues no longer provides for their patency. This, of course, presupposes a rapid assumption of capacity in the new capillaries for changes in calibre observed in normal capillaries. Such changes have been referred to in the earlier discussion of vasodilatation in inflammation.

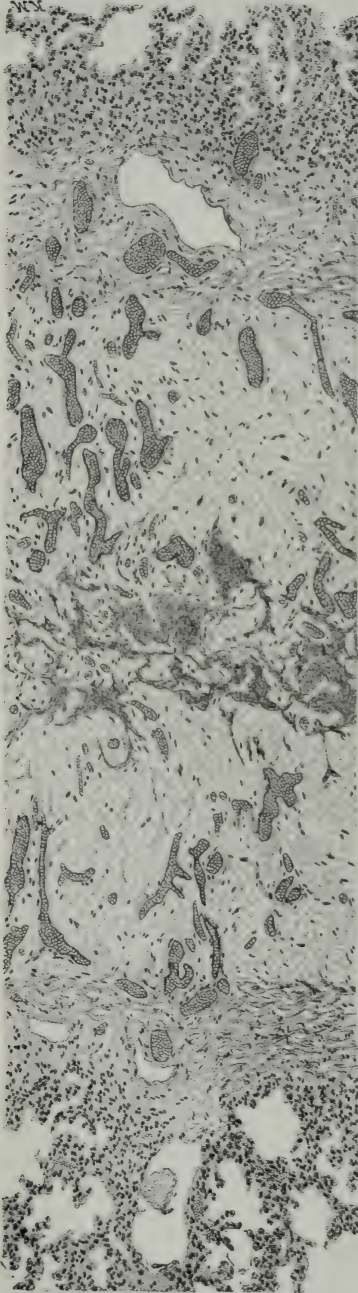


Fig. 76—Formation of adhesion in interlobar pleura. Organization has proceeded from both pleural surfaces and meets in the middle, where a small amount of fibrinous exudate is still present.

The gross appearance of a scar is familiar. In its earlier stages it is red, soft and almost coextensive with the original inflamed area. It gradually becomes paler until it is pearly white, at the same time decreasing in size, and contracting until it is likely to be smaller than the original injured area. With the shrinkage comes increased density. If situated in an area where a distending force is applied, the scar may subsequently stretch. Thus, abdominal scars, if the incisions be not repaired so as to provide adequate muscle support, may stretch and permit of the formation of hernial projection of abdominal contents. Scars in tissues over joints, cicatricial adhesions between joint surfaces, adhesive bands in pericardial, peritoneal or pleural cavities may stretch so as to provide no impediment to function.

Adhesions constitute an important manifestation of scar formation. Fibrous adhesions occur as the result of inflammation of serous surfaces. In the pleura and pericardium, an inflammation of visceral sheets is communicated to the parietal membrane and vice versa; inflammations may thus involve the entire sac. In the peritoneum, inflammations may be localized to small areas but by contact involve apposing surfaces, such as those of a few coils of gut or coils of gut and parietal peritoneum. The cause may be bacterial or chemical, or as is frequently the case in the peritoneum or omentum, the result of surgical trauma. Regardless of the general type of the exudate, the surfaces show fibrin deposit, and if the fluid exudate be removed or absorbed, the fibrin of the apposing surfaces comes into

contact and a loose fibrinous adhesion is formed. Granulation proceeding from the two surfaces meets and a somewhat firmer adhesion is formed. As organization goes on to cicatrization, the scar tissue unites the two surfaces by a firm, fibrous union, the fibrous adhesion. The ultimate condition may vary from a few areas, often stretched into fibrous bands by the movements of the viscera, or may be seen as an extensive adhesion which in the case of the pleura or pericardium may completely obliterate the sac. Such obliteration of the pericardium may result in serious functional disturbance of the heart; in the peritoneum it may lead to limitation of intestinal motility; in joints it may restrict or completely inhibit motion.

Reaction to Foreign Bodies.—In the course of surgical operation, it is not uncommon that non-absorbable suture or ligature material may purposely be left in the operative field. Foreign bodies also gain access to the body by accidents of various kinds. Experimental study of inflammation has utilized foreign bodies, such as silk sutures, masses of agar and other substances. In spite of the fact that these materials are introduced without bacterial contamination, inflammation results. The early examination of the lesions produced experimentally, shows traumatic hemorrhage and a moderate amount of vascular dilatation, and an exudate of leucocytes, serum and fibrin. This is followed in the course of twenty-four hours by the reaction of the fixed tissues. Lymphocytes, endotheliocytes, sometimes plasma cells and others of similar nature put in their appearance. These cells outnumber the leucocytes except when infection is simultaneously present. The cells migrate toward the foreign body, and at about the same time the earlier signs of granulation appear with the multiplication of fibroblasts and the formation of new capillaries. Small fragments of the foreign material may be taken up by mononuclear phagocytes and carried away, but the bulk of the foreign substance remains in situ. In many cases foreign body giant cells occur. Studies of fixed tissues indicate that these cells originate by fusion of a number of endotheliocytes. The older idea that the giant cell is formed by multiplication of nuclei of an endotheliocyte without division of the cytoplasm, is no longer accepted. Lambert has produced these giant cells in tissue cultures. The foreign body giant cell shows multiple nuclei, usually of vesicular character and resembling rather closely those of the endotheliocytes. As the giant cell matures, the nuclei tend to condense, and may show little remnant of the vesicular character. The cytoplasm

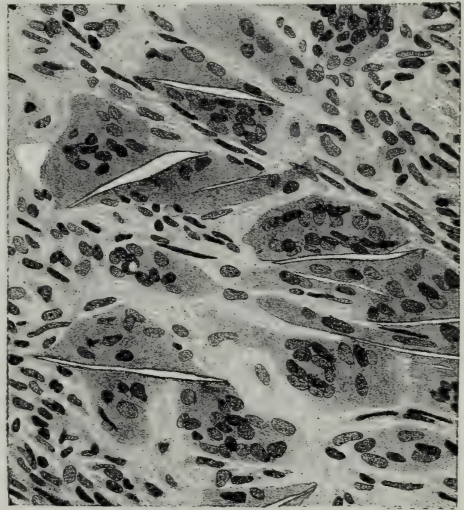


Fig. 77—Foreign body giant cells formed about cholesterol crystals, which have been dissolved in preparation and are represented as slits.

is closely apposed to the foreign body, and if the latter be small enough, it may be completely surrounded by cytoplasm. Thus, the foreign body giant cell has essentially the same phagocytic properties as the endotheliocytes from which it originates. Cells of the same sort may occur in any area of granulation, provided sufficient foreign or dead material be present to stimulate their formation, but as a rule, they are most commonly found in those reactions which occur as the result of foreign body implantation. Not only do they form about foreign bodies introduced from without, but in instances where crystals are formed in the body, the secondary formation of giant cells enclosing the crystals

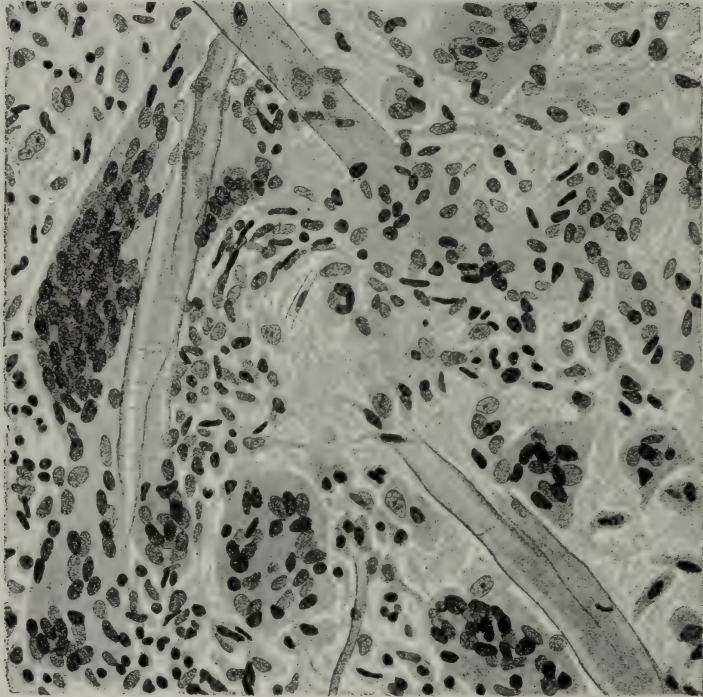


FIG. 78—Foreign body giant cells formed in response to the presence of insoluble suture material.

is not uncommon. Destruction of tissues leaving a considerable amount of necrotic material, which is not liquified and absorbed, may also be followed by foreign body giant cell formation about the fragments of necrotic material. These cells may remain in situ for a considerable time, but in the usual experimental lesions the ingrowth of granulation tissue soon displaces them. Granulation progresses into very close apposition to the foreign body and in the case of sutures, such as those of silk, penetrates between the fibrils of the suture material. Following this infiltration of granulation tissue, cicatrization occurs. Thus, the foreign body becomes encapsulated by cicatricial tissue. If the foreign body be of absorbable material such as catgut, the early reaction occurs in practically the same way, but as the ferments destroy the gut, this is dissolved and absorbed. Nevertheless, the process of replacement by granu-

lation tissue goes on in the same manner, and in the situation originally occupied by the ligature a small scar appears. The same general principle applies to non-infected areas of necrosis, as described in connection with infarction. The reaction is essentially the same as that to a foreign body except that giant cells are not commonly encountered in infarcts. The growth of granulation tissue progresses so as to form a band around the necrotic area, which upon subsequent cicatrization constitutes a fibrous capsule. If the



Fig. 79—Tongue of rabbit on third day after incision with knife. Line of incision shows remnants of hemorrhage, deep necrosis, fibrin formation. Reaction is noted about margins of wound. Epithelial proliferation and downgrowth are apparent.

necrotic area be small in extent, the granulation tissue may entirely replace the necrotic area and the final result be a complete cicatrization.

Healing of Wounds.—If a wound be inflicted aseptically and no infection occur subsequently, the process of healing is very closely similar to that about a foreign body. The wound causes a certain amount of hemorrhage, and necrosis of tissue through which the instrument has passed. After the edges of the wound are brought together, the reaction of inflammation appears in the margins. Thus, in even the cleanest wounds a small area of reddening is found shortly afterwards. Microscopic examination shows the early signs of inflammation in the form of vascular dilatation and exudation of a few leucocytes, and

serum, and fibrin formation. Endotheliocytes appear and granulation tissue is rapidly formed. The granulation starting from each side of the wound soon meets, so that in the wounded area there is a fused mass of granulation tissue. The ferments, the endotheliocytes and leucocytes dissolve the exudate and remove the necrotic tissue, so that in the course of twenty-four or forty-eight hours little remains but the mass of granulation tissue with only a few leucocytes and endotheliocytes. This granulation is soon replaced by cicatrization and the wound is healed. The clean healing of wounds is referred to in the



FIG 80—Healed wound of rabbit's tongue. Surface epithelium is completely regenerated but shows deep position. Cicatrix occupies space of tissues destroyed in wound.

surgical clinic as healing by first intention. Such wounds, however, may break down because of bacterial infection, in which case the bacteria grow most readily in the loose tissues and blood of the wounded area, and suppuration occurs. Although essentially like an abscess the area is primarily open, and from it pus is discharged upon the surface. As the infection is conquered, granulation tissue grows into the open area, gradually fills it up, becomes cicatrized and the wound is closed as the result of healing by second intention. In certain cases it is advisable to reopen wounds that have become infected secondarily, to clean the surfaces and bring them freshly into apposition. Sometimes this results in healing by what is essentially first intention. This is the principle

of the operation, called debridement, used successfully during the Great War in the treatment of shell and other wounds, infected before having adequate surgical treatment. Infected wounds may be kept open until the bacterial content is reduced. Then the edges are brought together by suture and the wound heals after what was called in the Allied Armies, delayed primary suture. Healing under a crust or scab is referred to in the discussion of ulcer. Healing of the skin surface is discussed under regeneration.

Regeneration.—By this term is understood a reproduction of tissue identical with, or closely similar to, that which has been destroyed. Physiological regeneration occurs to replace cells which have been destroyed in the normal wear and tear of bodily activity. This goes on actively throughout life and results in complete restoration of the destroyed tissue. In old age, however, it is possible that part of the atrophy of tissues may be the result of faulty or incomplete replacement. The so-called pathological regeneration represents the process carried on in order to repair diseased processes or defects. Regeneration in this instance goes on according to the regenerative capacity of the type of tissue destroyed, and this capacity varies greatly with different tissues, is better in the young than the old, and in a general way is in inverse ratio to the amount of tissue destroyed. If tissues be destroyed which have a great capacity for regeneration, the defect may show ultimately a complete regeneration of original structure. As a rule, however, many tissues are involved in lesions of any considerable size, so that regeneration is rarely complete. As in granulation, the process of regeneration is limited to the actual repair of defects. It is only rarely that granulation itself exceeds the need for repair. It is more rare that regeneration goes on to excess, but in the case of surface epithelium, following prolonged irritation, the epithelial growth may so exceed the normal as to constitute malignant tumors. There is a general rule, with many exceptions, to the effect that the higher the degree of specialization of a cell, the less the capacity for regeneration following pathological processes.

The regeneration of *surface epithelium* is usually active and complete. In case of wounds involving only the surface epithelium, it is found that very shortly after infliction of the wound, the epithelium of the deeper layers, namely the malpighian layers, moves slightly over the uncovered connective tissue surface. Mitotic cell division results in the formation of intermediate cells, and finally of keratinized squamous cells. In the case of mucous membranes essentially the same process of regeneration follows. If the wound involve the underlying structures, either the tunica propria of mucous membranes, or the corium of the skin, the extension of the deeper layers of surface epithelium over the wound surface is not immediately observed, and the first evidence of regeneration is the multiplication rather than movement of the deeper cells. The proliferation may result in slight extension downward of the epithelial growth, so that irregular bands of epithelium are found within the granulation tissue. As the defect is filled by granulation tissue, the epithelium grows over the surface until it meets with that of the opposite side. During this period, in the case of skin, the intermediate layers are also formed

and keratinization proceeds from the margins. After the defect is entirely replaced, the epithelium covering it cannot be differentiated from other stratified squamous epithelium, except that the line between epithelium and underlying corium is not thrown into ridges or papillæ as is the case with normal skin, and the area is devoid of hair follicles, sweat glands and sebaceous glands, since these do not regenerate. Surface epithelium in other situations follows the same general rule. The surface of the endometrium undergoes complete regeneration after menstruation, pregnancy or curettage. In the bladder, the stratified structure is easily restored. In the case of the intestine and similar structures, the surface epithelium is likewise restored. If glands be involved in the wound, they are not likely to be regenerated from the surface epithelium, and if they be completely destroyed, they have little capacity for regeneration themselves. In those mucous membranes where the glands represent merely crypts, new cryptlike structures may be formed by the growth of the surface epithelium. When skin surfaces are restored through the application of Thiersch skin grafts, the graft carries to the new area remnants of glandular structures and these may continue to grow so as to form oil glands, sweat glands and hair follicles. Glandular epithelium, considered as a whole, does not regenerate very readily. In fact, reproduction of destroyed glands from remaining gland cells is very uncommon. On the other hand, provided the ducts remain, they may take on what is essentially an embryological function of growth so that the ducts extend, enlarge at the end and reproduce glandular structures similar to, and sometimes identical with, those that have been destroyed. This is well exemplified in the liver where destruction of parenchyma, provided it involve connective tissue supporting framework, is not followed by regeneration of the essential liver cells, but a proliferation of bile ducts occurs, which sometimes forms not only club-shaped extremities made up of cells resembling liver cells, but may reproduce lobules somewhat similar to those of the normal liver. In the case of salivary glands, tear glands, and even in the breast, regeneration of glandular structure from preëxisting ducts may be functionally adequate and almost complete morphologically.

In the term *endothelium* we include the lining cells of blood vessels, lymphatic vessels and the larger serous cavities of the body. From the consideration of the formation of granulation tissue, it will be seen that vascular endothelium has great capacity for proliferation and regeneration. Lesions involving larger blood vessels, such as thrombosis, are completely covered by endothelium. Defects of serous membranes, produced by trauma or by inflammation, are rapidly lined by newly formed endothelium. The first change seen is a spreading out of the remaining endothelium so as to cover the margins of the thrombus or inflammatory exudate, rapidly followed by cell multiplication so that the areas are soon covered. The cells at first are cuboidal in character and only subsequently undergo flattening to resemble the normal type of surface endothelium.

As can readily be understood from the discussion of organization, the *fibrous connective tissue* of the body regenerates with extreme readiness. The

necessity of closing in defects determines a growth of connective tissue slightly in excess of that originally present. When scars are formed, the scar tissue is often quite indistinguishable from preëxisting connective tissue. In the case of skin, the only differentiation between scar tissue and preëxisting connective tissue lies in the fact that the scar tissue contains none of the skin glands and is covered by epithelium without papillæ. Elastic tissue represents a differentiation of connective tissue. There are no cells which have as a specific function the formation of elastica. Nevertheless, in healed areas elastic tissue may appear to have regenerated. This is the result of differentiation of newly formed connective tissue. The regeneration of *fat* may originate in some preëxisting fat cells which remain, or may represent a transformation of regenerating connective tissue cells which assume the special function of fat formation. The regeneration of true fat cells may go on actively, and indeed, may sometimes lead to the formation of multinucleated giant cells. Regeneration proceeds from the remnant of fat cells, including those without fat content but with intact nuclei. The fat is deposited first in minute globules which subsequently fuse to form the single large globule of the adult fat cell. In this early stage, the fat cells with their numerous small globules are morphologically identical with embryonic fat cells. In other cases fat may be formed in connective tissue where there were no preceding fat cells. This represents a functional differentiation of fibroblasts and their successors to form fat tissue. In these instances too, the fat is deposited first in small globules, which subsequently merge to form the large signet ring cells of fatty tissue. The regeneration of fat tissues may, however, be much restricted by the mechanical limitation of dense cicatricial tissue.

The regeneration of *cartilage* occurs by activity of the cells of the perichondrium. Their multiplication gives rise to forms morphologically similar to the fibroblasts. Cell processes increase in size and multiply to form a fairly solid mass of these cells. As these increase in number, the cytoplasm of adjacent cells fuses to form a solid, hyaline mass or matrix. The nuclei are surrounded by a thin rim of cytoplasm, enclosed in small lacuna. In regenerating areas, transition stages between the fibrillar form of these cells and true cartilage cells in matrix are observed. Cartilage may similarly be formed by cells of the periosteum and of the endosteum, as well as from connective tissue which apparently originally had no connection with cartilage.

Bone formation in newly formed cartilage follows the general rule seen in ossification of cartilage in early life, namely, the ingrowth of osteoid tissue, which replaces the cartilage and finally becomes calcified with true bone formation. New bone is formed by the activity of cells of the periosteum and to a certain extent of the endosteum. These cells grow in the form of morphologically undifferentiated cells, similar to those in regenerating perichondrium. They proliferate and form numerous fibrils, which intermingle with one another so as to constitute a loose network. In the formation of spongy bone, the cells finally lodge in spaces between the fibrils. Subsequently, the fibrillar material becomes homogenized and calcified so as to form spongy bone. As the calcare-

ous material is deposited, the differentiation into Haversian systems occurs, and subsequently osteoclasts may appear and rarify the new bone to proper proportions. The formation of compact bone follows essentially the same program, originating in the periosteum, as a rule, by the laying down of parallel rows of cells which produce fibrils, become calcified and form compact bone layer after layer. The marrow may also regenerate from preëxisting marrow cells and blood vessels. This follows the general process whereby marrow is formed in embryonic bone. The capacity of cartilage and bone for regeneration is great. In each case, there is little anatomical or functional differentiation of the generating cells. It is true that they form very definitely outlined areas, but the final differentiation depends either upon homogenization (hyalinization) of fibrils or upon calcification. When bones are fractured, hemorrhage occurs about the fractured ends. Growth of granulation tissue replaces the hemorrhage and disposes itself about the fractured ends. The granulation becomes firmer by calcification and irregular ossification to form a dense mass called callus. Callus appears about the periosteum (periosteal or ring callus) between the ends of the fracture (intermediary callus) and for a short distance up and down the marrow cavity (internal callus). The excess of callus, the provisional callus, is reduced in amount as the granulation tissue cicatrizes, and the definitive callus, between the bone ends, is converted into true bone. The failure of fractured bone to unite in old age is an example of the inferior power of regeneration that is found in later life.

There is but little difference between the capacity of *smooth muscle* and *striated muscle* for regeneration. Studies of injuries to the smooth muscle of the intestinal canal, and of other situations, show that following injury there is little or no regeneration of the smooth muscle cells. The wound is healed almost entirely by cicatrization.

The study of the regeneration of striated muscle, includes the myocardium and skeletal muscle. Our own experimental studies of attempts at regeneration of cardiac muscle, following such an injury as infarction, led to the conclusion, in conformity with that of the majority of workers on this subject, that there is no evidence that cardiac muscle undergoes actual regeneration following traumatic or other injury. Very rarely mitotic figures may be found in the muscle nuclei, and occasionally the ends of injured muscle show the presence of a number of nuclei resembling somewhat the formation of multinucleated giant cells. In no instance, however, was actual regeneration observed. A. J. Smith similarly found no clear cut attempt at regeneration on the part of human cardiac muscle. The same appears to be true in regard to regeneration of cardiac muscle following toxic necrosis. The work of Loeb and Fleischer, of Christian, Smith and Walker and of Anitschkow, indicates that myocardial regeneration forms no important part or no part at all in the healing of myocardial injuries. A recent study by Gierke offers evidence in support of myocardial regeneration, but examination of his figures is not convincing that the changes are not a part of cicatrization. Skeletal muscle may show very much more active attempts at regeneration. Following injury, there

is a certain amount of retraction and swelling of the living end of the muscle fiber. An increase in the number of nuclei rapidly appears as the result of multiplication of the nuclei underlying the sarcolemma. This apparently is usually the result of direct division of the nuclei but occasionally mitotic figures are found. From the margin of the muscle fiber, usually a short distance from the seat of injury, small processes of sarcoplasm branch out. These may be club-shaped or pointed and usually contain numbers of nuclei. In favorable cases where the defect is not too large, the muscle sprouts or buds coming from adjacent ends, may meet and lead to the formation of well differentiated and functional muscle fibers. The nuclei in part disappear and in part move to-

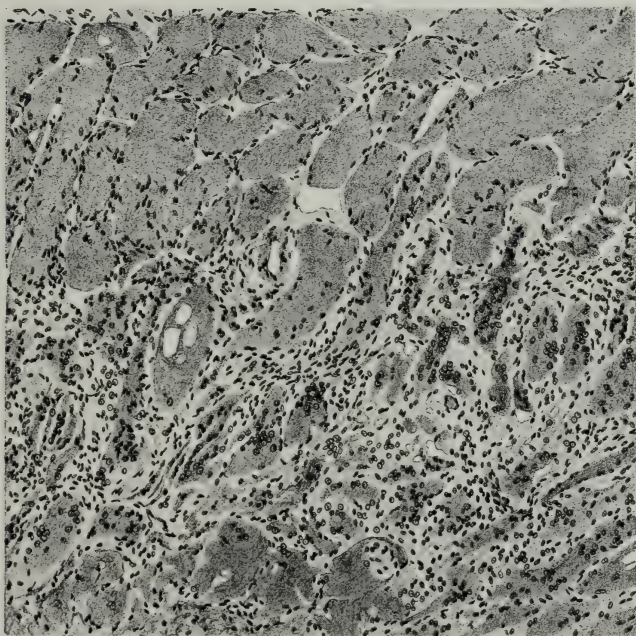


Fig. 81—Regeneration of skeletal muscle following Zenker's necrosis. Muscle giant cells are numerous and in left lower part of field muscle buds can be seen.

ward the sarcolemma. Longitudinal striation appears first and is followed by the appearance of transverse striation. Whether the sarcolemma is formed by the muscle or by the adjacent connective tissue is in doubt, but the majority opinion is that it is contributed by connective tissue. Occasionally where large areas of muscle are destroyed, a different type of regeneration is observed. Isolated cells resembling the embryonic myoblast appear, become elongated, fuse with adjacent similar cells, and ultimately by further differentiation are formed into muscle fibers. It is not likely, however, that large defects of muscle may be filled in by newly formed striated muscle. When muscle injury occurs, the greater part of restoration depends upon scar formation which produces adhesion of the injured ends and ultimately, when the scar is fully formed, a muscle which may function almost as well as normal.

Regeneration of nerve tissues will be discussed as it affects the supporting tissue of nerve substance or the neuroglia, the ganglion cells and the nerve fibers. Studies of regeneration in injuries of the brain in animals, show that the neuroglia regenerates with little difficulty. In fact, it may fill up a defect in very much the same way that connective tissue does in other organs. Where a brain injury involves the white matter, there may be regeneration of the nerve fibers beyond the point of injury. This regeneration follows much the same rule as that of peripheral nerves to be described subsequently. Injury to ganglion cells is not followed by any regeneration whatever in higher animal life. While regeneration may occur to a moderate degree in lower forms, such as reptiles and amphibia, the phenomenon has never been conclusively proven in higher vertebrates. Regeneration of peripheral nerves has been carefully studied both in man and in experimental animals. Regeneration of this sort depends upon preservation of integrity of the ganglion cells contributing the nerve fibers. When injury to the nerve occurs, degeneration follows. This extends along the central end to the next node of Ranvier, but occasionally may extend through several more segments. The degeneration extends distally to the termination of the nerves. It affects both the axis cylinder and the sheath of Schwann. This Wallerian degeneration is described more fully in the chapter on the central nervous system. Two views exist as to the regeneration of the axis cylinder. The generally accepted view is that regeneration proceeds entirely from the central end of the neuron. The axis cylinder elongates and passes through the injured area to the old distal tract. It is accompanied by new medullary sheath, provided in all probability, by cells of the original sheath, which seem to be stimulated to proliferation by the degenerate axon (Ingebrigsten). Meeting the degenerate distal nerve, the axis cylinder follows this line to, and including, the terminals. New medullary sheath is formed and regeneration is complete. The beautiful studies, by R. G. Harrison, of the growth in vitro of embryonic nerve tissue, strongly support this conception of regeneration. He regards the growth of axis cylinder as a form of protoplasmic movement, or ameboid outgrowth of the cytoplasm. The sheath cells proliferate and, as the axis cylinders grow, become arranged in tubular fashion. Apparently, the reproduction of new myelin is the result of combined action of axis cylinder and the sheath cells, since no myelin is formed until the axis is present. Spielmeyer, on the basis of Bethe's work, is of the opinion that the regeneration of axis cylinders is due to the activity of cells which he calls neuroplasts, derived from sheath cells. Harrison, however, in a subsequent study, maintains that the sheath cells have nothing to do with the formation of the axon.

In case of amputation where no further function of the nerve is required, it is common for the degeneration of the central end to extend as far as the ganglion cell and sometimes involve the latter in degeneration or atrophy. In certain cases, however, growth of nerve fibers continues in the stump and gives rise to intricate masses of nerve fibers, called the amputation neuroma. These structures are explained much more satisfactorily by the theory of

centrifugal growth of fibers than by the Bethe-Spielmayer hypothesis. Regeneration may be hastened by approximation of the severed ends of nerves; the greater the space to be bridged by regeneration, the slower the process and the less likelihood of complete restoration.

The essentials of the regeneration of *blood vessels* have been described in connection with granulation. Injuries to vascular areas show replacement of blood supply by the multiplication of capillaries. These are easily provided with adventitia by the accompanying multiplication of connective tissue cells. It is claimed that muscular regeneration may also appear, but this is not proven. Injury of larger vessels is not followed by regeneration of the vessels themselves. Circulation may be reestablished by collateral communication extending through capillaries and slightly larger vessels. In the case of obstruction to circulation by thrombosis, the process of canalization may occur as described in the chapter on circulation. Capillary lymphatics may regenerate in a manner similar to that of the regeneration of blood capillaries. The new formation of larger lymphatics from older lymphatics of the same type does not occur. Blood may be destroyed readily either as the result of hemorrhage or by the influence of some toxic material. Following hemorrhage, the blood cells may be restored to normal within the course of a few days, up to ten days or two weeks. When hemorrhage is severe and there is an accompanying depression of blood formation, complete regeneration may be delayed for a longer period. Destruction of blood by poisons such, for example, as carbon monoxide, or nitrobenzol or the toxic products of infectious disease, may be more or less rapidly restored. The blood as it circulates in the vessels is an adult tissue. The cells normally found in the circulating blood are no longer capable of multiplication so that restoration of the cellular element depends upon the bone marrow and lymph nodes. Poisons which may destroy blood in circulation may also depress or destroy bone marrow. If the latter occur, regeneration is slow. If the bone marrow be not markedly damaged, or if following injury to the circulating blood, it remain normal, multiplication of the various hematogenous cells goes on and results in delivery into the blood of adult cells. If multiplication in the bone marrow be rapid, immature forms of cells may be discharged in the circulating blood, so that following certain injuries we may find myelocytes of various types, nucleated red blood corpuscles and large lymphocytes (see Sabin).

In a general way it may be seen from the foregoing, that regeneration occurs with varying degrees of readiness in connection with different types of tissue. Aside from the inherent capacity of a tissue to regenerate, there are numerous other factors which play a part in regeneration following injury of inflammatory or other origin. It is easily understood that the larger the area of injury, the less likelihood is there of adequate regeneration. In these instances, cicatrization fills the defect. Nutrition plays an important part in the regeneration, so that in individuals who are improperly nourished, either as the result of actual starvation or because of diseases which interfere with assimilation and metabolism, regeneration may be very much decreased. As Morgan points out,

growth may be regulated by many factors other than oxygen and food supply. The regeneration of animal tissue depends to a considerable degree upon the age of the individual. In early life regeneration is undoubtedly carried out with much greater effectiveness than in late life. As age advances, the capacity for regeneration is much reduced. In the lower forms of animal life, cellular differentiation is not carried out to the same degree as in higher forms, so that in the lower animals regeneration may be active and complete. The same is true in regard to the lower vegetable forms. In the higher vegetable forms, regeneration follows much the same rule as in the higher animals. After tree branches have reached adult size their destruction is not followed by regeneration; new shoots from the trunk may form new branches but this is not a regeneration of the original branch.

Chronic Inflammation.—Marchand defines chronic inflammation as a process which shows prolonged exudation and prominent tissue proliferation, particularly of the vessels and supporting tissues; this originates either in an acute inflammation or independently of it, and develops gradually as the result of continued injury. The chief indication of chronicity in inflammation is the formation of notable amounts of connective tissue. All chronic inflammations are essentially productive. If, however, the connective tissue be the sign of chronicity in inflammation, there arises the question as to how one may distinguish between chronic inflammation and cicatrization. The latter condition represents complete healing and quiescence of the process, but in chronic inflammation it is necessary not only to identify connective tissue growth, but also to find in the area some of the coincident changes of inflammation. In certain instances these consist very largely of the presence of those cells which appear in the later stages of acute inflammation, namely, the lymphocyte, the endothelial cell, and the plasma cell. In inflammations of the intestinal tract, especially of the appendix and of the cecum, numerous eosinophiles are present in addition to the cells just enumerated. In parenchymatous viscera the most common cell to be found in connection with the fibrous tissue is the lymphocyte. Lymphoid foci of considerable size may be found. In addition the parenchymatous cells show considerable degeneration. Inasmuch as the process is long standing and progressive, it is commonly the case that there is not only cloudy swelling but also fatty degeneration. Not infrequently atrophy of the parenchymatous elements is also observed. In certain instances, chronic inflammation must be regarded as a process of cicatrization which is continuous, because of the repeated appearance or prolonged presence of the causative agent. The appearance of chronic rather than acute inflammation is sometimes determined by the site of lodgment of the irritant. For example, the tubercle bacillus in the lung most frequently gives rise to a chronic inflammatory process, but when implanted in the meninges commonly causes an acute meningitis. There are, however, differences in resistance of given tissues, and differences in number and virulence of infecting organisms. Therefore, it can be understood that the presence of chronic inflammation represents, as does acute inflammation, a sort of balance or ratio between virulence on the part of

the causative agent and resistance on the part of the organ or tissue. In general then, it may be said that chronic inflammation may be produced by causes which are low in virulence, by great resistance on the part of host in the presence of causes of greater virulence, by failure of the organism to remove an irritant which may thus act over a long period of time, or as the result of frequent attacks of acute inflammation. The infective granulomata including certain diseases as tuberculosis, leprosy, syphilis, actinomycosis, glanders and others, are likely to give rise to chronic inflammation in most situations, because of the low grade of virulence of the infecting organism. In certain cases, infection by organisms which produce acute suppuration may be followed by failure to remove the cause and result in chronic exudative processes. An

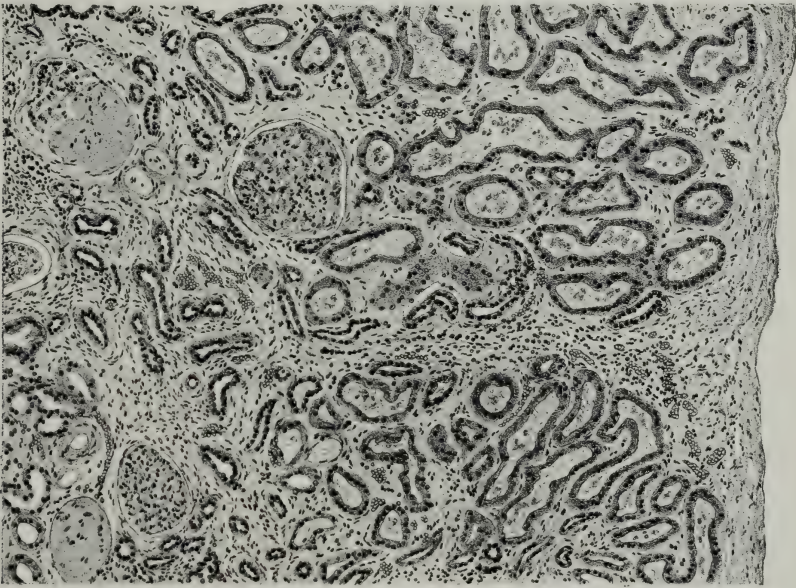


FIG. 82—Chronic nephritis. Note the marked increase of connective tissue between the tubules and the late stage of cloudy swelling of the tubular epithelium.

example is seen in cases of furunculosis, which probably because of diminished resistance on the part of the individual, may become chronic in course. The individual furuncle may show distinct indications of chronicity, and the reinfection of the individual is a further indication of decreased resistance. Of the greatest importance are the chronic inflammations seen in parenchymatous viscera. Such inflammations are likely to be the result of the absorption of toxic agents of some sort. These may include bacterial toxins as exemplified in cases of chronic parenchymatous inflammations of viscera following long standing, low grade inflammations, especially in cryptic situations such as the tonsils and around the teeth. Ingested poisons of various kinds may produce similar manifestations including such substances as alcohol, lead, arsenic and other drugs. The same condition may be produced by poisonous substances in the body as for example, in chronic rheumatism, gout, cases of prolonged intestinal

intoxication, prolonged chronic nephritis and other similar diseases. Chronic inflammations are also likely to result from prolonged mechanical injury. Thus, ulcers of the tongue and lip may result from the irritation of sharp edges of teeth. The same may be due to the heat and irritation of the smoke of a pipe, and body surface irritation by ill fitting clothing such as shoes, etc. Infection with vegetable parasites higher than the bacteria, including the yeasts and fungi, more frequently give rise to chronic than to acute inflammation. Similarly infection by animal parasites, such as the *trichinella spiralis*, more commonly produces chronic than acute inflammation.

The local signs of chronic inflammation are essentially the same as acute inflammation, but are present usually in a very much slighter degree. The swelling, however, instead of being soft is likely to be distinctly firmer and the part is said to be indurated. Disturbance of function may be very much more severe in cases of chronic inflammation, although this is not always true. Nevertheless, the disturbances of function, since they are prolonged over considerable time, may be of much more serious moment to the organism than are the disturbances of function seen in acute inflammation. This is particularly true of the parenchymatous viscera such as the kidney, liver and heart. Retention of waste products in acute nephritis may be serious, but if the patient recover no permanent damage may ensue. On the other hand, similar retention in the case of chronic nephritis prolonged over a considerable time, is likely to lead to long standing and irreparable damage. Circulation may be interfered with for a short time by an acute myocarditis, but if the myocarditis become chronic, the circulatory disturbances may lead to permanent changes in the other viscera. Chronic inflammation may also be of serious import in respect to the origin of malignant tumors. Regeneration of epithelium, particularly in connection with chronic ulcers, and sometimes possibly in connection with chronic inflammation, as for example, cirrhosis of the liver, may ultimately become unlimited and lead to the development of malignant epithelial tumors or cancers.

Subacute Inflammation.—There must certainly be stages in the process of inflammation in which there is to be found a transition period between acute inflammation and chronic inflammation. The demarcation of this period is extremely difficult because the transition from exudative to proliferative types of inflammation is by no means sharply defined. In a sense, the term subacute inflammation may frequently depend entirely upon the personal equation of the observer. Similarly, the finer division into subchronic inflammation as differentiated from subacute is extremely difficult. Nevertheless, if exudative inflammation be still present, and proliferative changes have occurred to a point indicating chronicity of the process, the term subacute is usually employed. If, on the other hand, the chronic changes be well advanced with only a slight remnant of exudative change, the term subchronic is frequently employed. Thus, in those instances where there is a considerable connective tissue growth associated with the presence of numbers of lymphocytes, endotheliocytes, and plasma cells, the condition is usually considered as subacute or subchronic, depending upon the amount of connective tissue growth. Many

pathologists, however, prefer to make no such differentiation and would call a process of the sort just indicated chronic rather than subacute or subchronic. Inasmuch as a pathological diagnosis must indicate the essential nature of the process, this differentiation seems to us quite justified. It is possible to indicate as subacute or subchronic, inflammations in which a few polymorphonuclear leucocytes may still be present. This cell is distinctly more characteristic of exudation than the other cells noted and its presence leads to the supposition that the acute stage of the inflammatory process is still in evidence. These types of inflammation must be considered as progressive in the same sense as are the chronic inflammatory processes. In the subacute forms the probability of self-limitation of the process is greater than in the chronic.

Inflammation in Avascular Tissues.—Inflammation may affect such avascular tissues as cornea and lens of the eye, parts of cartilage and the free edges of heart valves. Experimental inflammation of the cornea has been studied by Grawitz, Leber, Councilman and others, and their results may be applied to other avascular tissues. Traumatic or bacterial injury affecting only the epithelial cells of the cornea is followed by regeneration, which may for a short time be slightly in excess of the need for replacement, and result in multiplication of layers. Aseptic injury of the corneal tissue may result in multiplication of corneal corpuscles to fill the defect. More serious injury, such as may be produced by injection of pyogenic bacteria, leads first to necrosis in the immediate area, multiplication of bacteria which penetrate into the tissue spaces, subsequent swelling, degeneration and death of neighboring cells and fibers. Only after several hours have elapsed is neighboring vascular reaction observed. The marginal vein and small vessels become dilated and grossly visible as an area of hyperemia at the margin of the cornea. This delay in vascular reaction is due, presumably, to the time necessary for passage of the bacterial poisons into the peripheral tissues. Microscopic examination shows typical vasodilatation, margination and emigration of leucocytes. As an evidence of chemotaxis, the leucocytes migrate directly and rapidly to the point of injury, and may take part in the formation of an abscess. If the injury be eccentrically placed, the part of the margin nearest it, shows the most marked inflammation. In unfavorable cases, the inflammation may extend widely in the eye, especially in those cases where the local lesion perforates the cornea and infection extends into the chambers. In favorable cases, repair occurs by multiplication of corneal corpuscles, and of surface epithelium. In the more severe cases, granulation proceeds from the margin by proliferation of capillaries and fibroblasts, which grow in toward the injury. In either case there remains an area of opacity and, after cicatrization is complete, some of the new vessels may remain permanently in the cornea. Inflammations of heart valves occur usually near the free edge, as thrombi. Leucocytes infiltrate from the circulating blood and after a time from the vessels of the valves. Organization originates from the connective tissue and the blood vessels of the leaflets. After cicatrization, the valves are likely to show some remaining and permanent new vessels, which extend from the original vessels to the cicatrix.

Ulcer.—The ulcer may be defined as an interruption of surface continuity with accompanying inflammation. Certain authorities believe that in order properly to be qualified as an ulcer, the inflammation must be suppurative, but the broader conception is not limited in this way. Ulcers may be found on any surface of the body and may be due to traumatic destruction of the surface, or result from degeneration, necrosis or inflammation in the neighborhood, which leads to the sloughing of the injured superficial tissue from the underlying parts. Ulcers of the skin and mucous membranes are very common. On the skin surface they may result from direct physical injury of various kinds. In the mucous membranes of the mouth they may be due to laceration by substances taken into the mouth, or by sharp edges of carious teeth. In the intestinal canal they are most commonly the result of inflammation of the gut wall, with subsequent necrosis and sloughing of the epithelial and sometimes of the submucous lining of the gut. In certain other mucous surfaces, as for example, the gall bladder and the genito-urinary tract, ulcers may result from abrasion by calculi. In any surface accessible to the exterior of the body, ulcers may be caused by direct trauma. Ulcerations also appear in the arteries as the result of breaking down and sloughing off of degenerative and necrotic portions of the intima and deeper parts. The necrosis is accompanied by surrounding inflammation so that ulcers in this situation meet the broader definition. The course of ulceration, that is as to whether it heals rapidly or slowly, depends upon the nutrition and reactive capacity of the tissue. One of the commonest chronic ulcers is that type seen on the leg of older people. These may persist for months or years, and the failure to heal is probably due to damming back of circulation incident to posture, to mode of life, or to general failure of the circulation. On examination, an ulcer shows the interruption of surface continuity. In those cases of ulceration of the skin and mucous membrane there is, after a short time, regeneration of the surface epithelium which attempts to grow in and cover the defect. Inflammation at the base depends in its nature upon the amount and type of infection present. If kept fairly clean, the base may show little actual suppuration. There is always a moderate amount of serous exudation which may dry on the surface so as to produce a crust or scab. If the infection underlying the crust be easily overcome, the crust formation may aid materially in healing. In the more prolonged types of ulcer, the base is likely to show, in addition to the serous exudation, considerable infiltration by the cells seen late in the course of inflammation, namely, lymphocytes, endotheliocytes, and plasma cells. Somewhat deeper, granulation is found proceeding with different degrees of activity. Gross inspection shows the small knobs of projecting capillaries and connective tissue which gives the name granulation tissue. Ordinarily, in a favorable case, the granulation proceeds until it fills the defect, is covered by epithelium and gradually cicatrizes. In other instances, granulation may be excessive in amount and form a projecting mass above the general level of the surface, the so-called exuberant granulation. The surface epithelium grows over such superfluous granulation with greater difficulty than if the granulation merely

fill the defect. The final healing is therefore delayed. If the excess of granulation be removed, surface healing is likely to proceed more rapidly and the final results be improved. Surface ulcers are, of course, subject to trauma. When applied to the delicate vessels of granulation, this is likely to cause hemorrhage which may appear on the outer surface or may simply infiltrate the tissue. Therefore, in old ulcers it is not uncommon to find phagocytic endotheliocytes in the base and in the margin, which contain blood pigment. If epithelial proliferation go beyond the normal, as may readily happen in chronic ulcers, it may become unlimited in character and lead to the development of carcinoma.

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CHAPTER IX

PRINCIPLES OF INFECTIOUS DISEASE

INTRODUCTION.

INFECTIOUS DISEASE.

FACTORS FAVORING THE INVADER.

ENTRANCE OF THE INVADER.

FACTORS FAVORING THE HOST.

THE COURSE OF INFECTIOUS DISEASE.

GENERAL MANIFESTATIONS.

FEVER.

LEUCOCYTOSIS.

PATHOLOGICAL EFFECTS.

SPECIAL TYPES OF INFECTIONS.

PYOGENIC INFECTIONS.

STAPHYLOCOCCUS.

STREPTOCOCCUS.

DIPHTHERIA.

TYPHOID AND PARATYPHOID FEVERS.

Introduction.—Infectious diseases include those diseases which are transmissible from one individual to others, either by direct contact, in which instance we deal with contagious disease, or by the mediation of inanimate carriers of infections, such as water, food, clothing, or of animate carriers. The inanimate carriers may serve as culture media upon which the organisms multiply or, as in the case of clothing, utensils or other fomites, simply act as inert carriers. The animate carriers may carry from host to host, or contaminate foods and waters, or they may serve as intermediate hosts in which a definite cycle of the parasite takes place. Human carriers may convey disease on hands or clothing, or they may harbor in the gall bladder, throat or other situation organisms to which they are temporarily or permanently immune, but which upon discharge are virulent for others.

Infectious diseases may be caused by bacteria, e.g., diphtheria, pneumonia; by higher vegetable organisms, e.g., sporotrichosis, actinomycosis; by protozoa, e.g., malaria; and by higher animal or metazoan parasites, e.g., trichinosis. Metazoan parasites, such as worms and insects are as a rule infestations of surfaces, intestinal, skin, etc., rather than infections entering into the body, although they may produce absorbable injurious substances as in the case of infestation by the fish tape worm, *dibothryophyllum latum*. In addition there are the filterable viruses, such as the organism of acute anterior poliomyelitis. There are also the *Rickettsia* which apparently cause Rocky Mountain spotted fever, typhus fever and perhaps other diseases.

In this chapter only the general principles of infection can be considered. The phenomena of resistance and immunity are covered in special texts. The pathology of many of the special infections must be sought in the sections on special pathology or in books and original articles on the subject.

Infectious Disease.—Infectious disease must be regarded as a reaction on the part of the host to the presence of pathogenic organisms. There is little doubt also that certain of the infectious organisms are acted upon by the host

so as to alter, at least temporarily, some of their biological characters. Philosophically then, disease may be looked upon as an interaction or mutual reaction of hosts and parasites. Although organisms may, by virtue of their physical presence, or by the elaboration of certain substances, produce some of the manifestations of the disease, yet the major part of the manifestation is due to the reactive capacity of the host. As pointed out in the chapter on inflammation, it is possible for organisms to enter a host and produce only local reaction. In a general way, such local reactions may be regarded as manifestations of disease, but it is commonly accepted that in the term infectious disease are included only those conditions in which there are important general manifestations in addition to, or independent of, local manifestations. These general manifestations may include a wide variety of conditions from simple malaise to the most profound exhaustion; there may be generalized cutaneous eruptions and various alterations in bodily metabolism and excretion; chills and sweats are common, but the most outstanding sign is fever. Infection which remains localized and therefore produces only local inflammation, is not likely to be accompanied by any of these symptoms or signs. The general manifestations are due to dissemination throughout the body of poisonous products of the organism, or of the organisms themselves in addition to their poisonous products. On this basis we distinguish sapremia, toxemia, septicemia, and pyemia. Sapremia results from the dissemination throughout the body of toxic products produced by saprophytic organisms such as grow in necrotic areas. Toxemia is due to dissemination of more or less clearly identified toxins resulting from the growth of parasitic, pathogenic organisms. In septicemia, organisms are present in the circulating blood in addition to the toxemia. This term is not synonymous with bacteremia which apparently occurs fairly often during otherwise normal life, without exciting any important symptoms. The term subinfection is sometimes used to indicate those transient bacteremias, especially originating in respiratory and intestinal tracts, which show little or no general disturbance. As the result of recent studies, it is believed that the mere presence of organisms in the blood is not necessarily of great importance, and that it occurs without symptoms and with greater frequency than has heretofore been thought. Pyemia signifies septicemia accompanied by the formation of multiple abscesses in various parts of the body. Etymologically pyemia means pus in the blood and with our present knowledge might well be abandoned; more literally descriptive would be some such term as productive septicemia. These terms offer an important classification of infectious disease. Infections may also be classified as acute or chronic. The acute infections are those resulting principally from such organisms as the pyogenic cocci, diphtheria bacillus, typhoid bacillus, pneumococcus, and a number of others. Chronic infections may be the result of pyogenic organisms, but are particularly well exemplified by such diseases as tuberculosis and syphilis. As has been pointed out in the opening chapter, infectious diseases are also classified depending upon their course; they may be continuous, intermittent, or remittent.

Infection simply signifies the successful invasion by parasitic organisms. Primary infections are those which occur without any decrease of resistance due to another infection. Secondary infections occur in individuals already suffering from infections of another nature. The latter is well exemplified in the secondary infection of a tuberculous cavity of the lung by staphylococcus. Terminal infections are those which occur near the fatal termination of some other disease, whether that other disease be of bacterial nature or of some other origin. Infections of this type are seen in the terminal bronchopneumonias and septicemias which occur in the course of certain chronic diseases. Mixed or multiple infections are not rare, and it is sometimes difficult to determine which infection is of greater importance. There is no doubt that one infection influences another existing at the same time and usually in a manner deleterious to the patient. Measles or lobar pneumonia may excite latent tuberculosis into activity. Latent syphilis may become active as the result of an attack of typhoid fever, and latent gonorrhea by an attack of tonsillitis. The removal of one chronic infection may favorably influence another, as seen in the relief of certain cases of pyorrhea alveolaris by the removal of infected tonsils, and in numerous other instances of multiple, chronic infections.

Factors Favoring the Invader.—Lower and higher forms of minute animal and vegetable organisms are generalized throughout nature, and the pathogenic members of these groups are limited in their distribution only by necessity for parasitism. Even those which require intermediate hosts for their life cycle or transmission are in the same category because of the widespread distribution of such intermediate hosts as mosquitoes, lice, ticks, and other carriers. The small size of pathogenic bacteria and protozoa aids in avoidance of detection, favors transportation in water, food and as particles in the air, and aids in penetration. Rapid multiplication, the formation of resistant spores and cysts, adaptability to different types of environment, ability to derive nutrition from various food stuffs, all favor the invading organism in maintenance of life, transportation, life under adverse circumstances and penetration. Their virulence varies in degree and is of importance in establishing disease. Virulence may depend upon deleterious substances produced by the bacteria or upon resistance to the destructive powers of the host, due to protective mechanisms of the invader. Their capacity to form ptomaines, exotoxins and endotoxins, aids invasion by reducing the resistance of the host. Not only may the whole protein of the bacterial body be poisonous, but destructive products of these proteins, the so-called split-proteins studied by Vaughan and Novy, are also highly toxic and undoubtedly can aid the invader. Once established, infection may lead to certain changes in the reactive capacity of the host called allergy, and the altered character of reaction is likely to manifest itself in increasing sensitiveness to the products of the organisms. It is possible also that the organisms, or their products, operating in conjunction with certain substances within the body, may produce a new toxic substance, the so-called anaphylatoxin, which is capable of decreasing general resistance.

Entrance of the Invader.—In order to enter the body, the organisms or their products must penetrate through one of the body surfaces, such as the skin, conjunctiva and the mucous membranes of the respiratory, alimentary and genito-urinary tracts. Invasion through the skin necessitates, as a rule, interruption of continuity as by traumatic injury, growth of organism in crypts of the skin, particularly hair follicles and sweat glands, and the bite of blood-sucking insects. Similar interruption of surface continuity of the various mucous membranes is of importance, but it is known that bacteria may penetrate the surface of the respiratory tract and of the alimentary canal without definite lesion of the mucous surface (see Moody and Irons). Certain organisms appear to enter almost exclusively through special surfaces as for example the pneumococcus in the respiratory tract, the typhoid bacillus in the intestinal canal, and the gonococcus in the genito-urinary tract. Indeed, organisms may be relatively harmless in some situations and extremely virulent in others.

Factors Favoring the Host.—The host is favored by the normal continuity of body surfaces. Various secretions, by their movement, may wash away infecting organisms, and in certain instances, by their chemical composition, operate against the organism. Defenses such as hairs in the anterior nares and ciliated epithelium in various parts of the respiratory tract, aid in filtering out organisms or in transporting them so that they can be expelled. The intelligence of the higher forms of animal life aids in the avoidance and elimination of infecting organisms. Intelligence leads to purposive voluntary movements, and in addition more or less involuntary movements of reflex character, such as sneezing, coughing, diarrhea, increased flow of tears, etc. may aid the host. Of utmost importance are cellular activities in the interior of the body, such as phagocytosis and the defensive process of inflammation. There are in addition the important so-called humoral defenses of the body. These include antitoxins which neutralize toxins, agglutinins which operate to favor deposition of organisms in places where they may be readily phagocytosed, precipitins which may throw out of solution poisonous protein substances, cytolytins which may kill and dissolve bacteria or other invading organisms, and opsonins which prepare bacteria and other particles for ingestion and destruction by phagocytes. The operation of the humoral factors is fully discussed in the textbooks on immunology.

It must be admitted that the normal activities of the body are not entirely an unmixed good when viewed from the point of view of infection and transmission of infection. Thus, the large body surface and the locomotion of the body as well as a multiplicity of other factors frequently bring the body in contact with infectious surfaces or invading organisms. Ingestion of food and water may bring pathogenic organisms into the body. The ready availability of the superficial orifices such as the nose, ears, mouth, anus, and genital orifices may favor the invader rather than the host. The body temperature, darkness and moisture of the interior, offer favorable conditions for the multiplication of organisms. There are certain structures in the body which are relatively

inactive such as the appendix vermiformis and crypts of the tonsils, where organisms find moisture, warmth, and darkness suitable for their development. The circulation of lymph and blood may favor widespread dissemination of organisms. Phagocytes containing organisms may spread infection by amoeboid motion or carriage in the body fluids, especially where the phagocytic activity is not sufficient to kill the ingested organisms.

The Course of Infectious Disease.—The exact moment of invasion of an infectious agent is difficult to determine, but in many cases of infectious disease, the time of exposure to infection can usually be determined within the limits of a few hours. Following the moment of invasion there occurs a period of incubation during which the host exhibits no symptom of infection. This period of incubation in some diseases is extremely variable, whereas in others it is relatively fixed. In diphtheria, incubation may apparently vary from twenty-four hours up to nine or ten days, and certain diseases show similar variation. In scarlet fever, on the other hand, the incubation period is very commonly five days, and numerous other diseases show a comparative fixity of incubation time. It has been suggested that when bacteria are planted in artificial culture media more or less distinct physical and chemical changes occur before growth becomes active. It is possible that the incubation period in the living animal represents somewhat similar changes preparatory to active multiplication. It cannot be necessarily assumed that the lag or latent period in growth of bacteria following implantation into new media, as studied in this country by Chesney and by Buchanan, is reduplicated in the stage of incubation in animals. Following the period of incubation, the less violent infectious diseases show a short period of prodromal symptoms in which headache, malaise, and other minor manifestations may appear. The next period, that of onset of disease or so-called invasion or effervescence, may be frank or insidious. Lobar pneumonia may develop within a period of a few hours and exemplifies frank onset. As a contrast, typhoid fever is likely to occupy a week or ten days between the period of prodromal symptoms and the full development of disease, thus illustrating insidious onset. That period during which the disease is at its height is called the fastigium or acme. Following the fastigium comes the period of decline or defervescence. This may be by crisis or lysis. Crisis is seen in approximately half the cases of lobar pneumonia, in which the decline occurs in a period of a few hours. Defervescence by lysis is seen in a large number of infectious diseases and is particularly well exemplified by typhoid fever in which several days, a week or more, may be consumed. Convalescence indicates that period during which the symptoms of disease have practically disappeared and the patient gradually recovers and is restored to normal. Most of the acute infectious diseases are more or less self-limited in their course. Thus, lobar pneumonia runs a course of seven to eleven days, typhoid of about three weeks, scarlet fever and diphtheria a few days. This means that with an individual of average resistance and an organism of average virulence, the defenses of the body conquer the forces of attack within a fairly definite period of time and recovery ensues.

Disproportion, in the form of too great virulence or too low resistance, may prolong the course of the disease, delay recovery, or result in death. Chronic infectious diseases exhibit no such regularity of development and course. In contrast to the acute infections, these are not likely to be self-limited, but progress until they have reached a point of such great severity, or of such complete exhaustion of the host, that death ensues.

Two of the most important general phenomena of infectious disease are fever and hyperleucocytosis.

Fever.—This term signifies a syndrome of which elevation of body temperature is the constant manifestation. Fever includes hyperthermia and a chain of other conditions varying in appearance or severity with the degree of temperature elevation, and including dryness of skin and mouth, herpes, decreased output of urine, respiratory disturbances, increased heart rate and nervous symptoms varying from minor muscle twitchings to active delirium. There are in addition important but not marked alterations of metabolism. Studies of fever in experimental animals have given conflicting and unsatisfactory results. The studies of fever in man have dealt with the infectious diseases and only in a general way is it possible to distinguish between the effects of the fever and of the underlying disease.

Mammals are homothermic or warm blooded as contrasted with the poikilothermic or cold blooded animals. Warm blooded animals maintain a temperature that is constant with a possible normal variation not exceeding 5 or 6 per cent. In man the normal variation may range between 36.3° and 37.5° C., with a diurnal rhythm from the minimum in the early morning to the maximum in the later afternoon (Benedict). In lower mammals the temperatures are usually higher and in birds may reach 43° C. The regulation of body heat is by the mechanism of thermotaxis, which properly balances the production and the dissipation of heat. Heat is produced by absorption of food, especially proteins, by the general chemical changes of metabolism and especially muscular work. It is dissipated by radiation, conduction and water evaporation. Circulation in the skin is therefore of the utmost importance in heat dissipation, since the blood flow to the skin aids both by radiation and conduction, and by sweating and evaporation, in assuring proper heat elimination. The thermotaxic center in the midbrain is apparently influenced by the temperature of the blood and by afferent sensory impulses, particularly from the skin. The involuntary regulation is principally in the direction of dissipation. Increased heat production occurs as the result of shivering or perhaps less noticeable activity of the muscles, by eating and by voluntary exercise.

Body temperature may be increased by high external temperatures, by violent exercise and by certain drugs and chemicals such as strychnin, caffeine, xanthin. Injections of sodium chloride solution may produce hyperthermia, which does not appear if calcium and potassium salts, as in Ringer's solution, be added. The hyperthermia of salt solutions made with old distilled water is probably due according to Hort and Penfold to the presence of minute

traces of organic matter, although this is denied by Yamakami. The latter finds that old or fresh distilled water produces fever because of hemolysis. The production of fever in this way probably also bears on the fever of malaria. These various forms of hyperthermia are not necessarily to be regarded as fever, according to the conception offered above.

The exact mode of operation of the causes of fever is unknown, and correspondingly the identity of the various causes ascribed is not clear. The poisonous products of bacteria produce fever. Products of protein disintegration, whether the split-proteins of Vaughan or other products, induce fever. Foreign proteins, when introduced parenterally often lead to fever, probably as the result of subsequent disintegration in the body. Water, hypotonic and hypertonic salt solutions induce hyperthermia. Allergic and anaphylactic phenomena are often accompanied by fever, although acute anaphylactic shock in animals usually produces a fall in temperature due to more profound intoxication than is present in the usual human cases. Lesions of the brain including cerebral hemorrhage, especially when it involves the ventricles, and traumatic lesions of the head, sometimes are accompanied by fever. There is also a so-called hysterical fever, not well established, supposed to occur in the neuropsychotic type of individual due to excitement. A reflex fever is said to occur as the result of painful excitation, as exemplified in biliary colic, but in spite of Roger's statement that it has been produced experimentally in dogs, it is possible that in man infection plays a part. The studies of Cramer indicate that disturbances of sympathetics and adrenal-thyroid relations may produce a distinct hyperthermia similar to that of heat stroke.

The toxic fevers do not occur experimentally if the spinal cord be sectioned in the cervical region or the midbrain be removed; therefore they are probably due to influences upon the centripetal part of the mechanism of thermotaxis. Lesions of head and brain probably operate directly upon thermotaxic centers.

Studies of fever in man are more or less complicated by changes incident to the causative process. Heat production has been studied in various infectious diseases. As an example, typhoid fever, according to DuBois, shows an increased heat production of 23 per cent. to 44 per cent. In six different diseases there was an average increased heat production of about 13 per cent. for each degree centigrade over normal. This increase is extremely small as contrasted with muscular exercise which may increase heat production 300 per cent. or more without inducing hyperthermia. Indeed patients may have fever and show no increase or even a decrease in heat production. Blood pressure may be increased, normal or decreased (see Kraus). The peripheral blood flow is increased in fever but not nearly to the same degree as occurs in normal individuals whose temperature is artificially raised to a comparable degree. The mechanism of heat dissipation is not thrown out of function in fever. Quoting Hewlett, "the febrile temperature is primarily due not to an increase in heat production or to an absolute inefficiency in heat dissipation but to a lack of adjustment between the two." The center is apparently either "set" for a higher level of temperature or in a state of altered excitability.

The respiratory quotient is about normal but may be increased in convalescence. Carbohydrate metabolism is normal, but fat metabolism is increased, much as it is in starvation. Protein metabolism is moderately increased, apparently with considerable destruction of body proteins. The body proteins can be protected by a high caloric diet rich in carbohydrates, and there is no satisfactory evidence that protein is necessarily destroyed by poisonous products of the disease. Thus, excess protein catabolism is probably partly due to starvation. Increases in output of uric acid, purin bases and creatinin usually accompany the increase in protein metabolism. Part of this is due to the protein destruction, but since Myers and Fine have shown an increased formation of creatinin from creatin in autolysis when temperature is increased, it is at least to be suggested that the increased output of creatinin in fever may be influenced by the body temperature. Koehler found the acid base equilibrium of the blood shifted toward the alkaline side in acute fever. This may not hold good for more prolonged fevers and acid intoxication may occur, probably due to disturbance of ketogenic balance resulting from the rapid consumption of carbohydrates. Thus, conditions for normal metabolism of fats are altered and the formation, from the excessive and imperfect catabolism of fats, of betahydroxybutyric acid, acetoacetic acid, and acetone may occur. It is by no means certain that increased metabolism is the cause of fever. On the contrary, the increased temperature may accelerate the velocity of the chemical reactions according to the law of Van't Hoff (see Boothby and Sandiford). Various products of protein cleavage have been held responsible for fever and upon injection may produce fever in experimental animals, but how they operate is not clear (Krehl).

Salt and water metabolism are usually altered. Chloride excretion is commonly reduced, except in malaria. Pneumonia is a striking example, with its salt retention during the disease and increased output after the crisis. Prigge found that following intravenous injection of salt in pneumonia, it disappears from the circulating blood with normal rapidity but its excretion in the urine is much delayed. With the salt retention there is a retention of water in tissues and blood, so that the latter is often distinctly hydremic. At the end of the disease the water and salt are excreted, the body weight is reduced and the specific gravity of the blood increased. With the hydremia it would be expected that heat dissipation would be favored by increased evaporation (Barbour), but this is not necessarily the case. Balcar, Sansum and Woodyatt bring evidence to support the hypothesis that water in the body exists as "free" water, and as "bound" water, the latter in combination with salts and colloids so as not to be available for excretion by lungs, skin or kidneys. Thus, even though the blood be hydremic there is a reduction in "free" water, so that heat dissipation by evaporation is seriously interfered with. Of such a nature are probably "thirst" fevers, "inanition" fevers of infants and salt, lactose and glucose fevers. Barr, Cecil and DuBois find, however, that in protein fever, which is comparable with fevers of infectious

diseases, there is "no evidence that the body is unable to mobilize water for heat elimination."

The mechanism of the chill, which often precedes fever is not understood, except that the chill is the precursor of rapid elevation of temperature, and apparently sudden changes in the conditions of thermotaxis may reverse the reacting mechanism, in this instance with chilly sensations. Conversely, when temperature suddenly falls as in a crisis, there may be flushing, sweating and general depression. Barr, Cecil and DuBois find that in chills produced by injection of bacterial proteins, there is an increase of heat production of from 75 per cent. to 200 per cent., in part due to shivering, and not associated with an increase of heat elimination. As fever appears the heat elimination increases.

The function of fever in combating infection is not clear. It is well known that high temperatures inhibit the growth of bacteria, but it is only in severe fevers that body temperature could have any definite influence in this direction. Temperatures high enough to produce any such effects are capable also of defeating the desired end because they may possibly lead to cloudy swelling of parenchymal cells. Fever produced by injection of proteoses and bacterial proteins is accompanied by mobilization of non-specific protease, decrease of antiferment, increase in non-coagulable nitrogen and amino-acids, decrease of proteases, and increased flow of lymph from the thoracic duct (Jobling, Peterson, Eggstein), but although these aid in combating infection they are not produced by the fever itself. The serum changes and the fever apparently have a common cause. Hewlett points out that moderate elevation of temperature may aid in the production of antitoxins, agglutinins and bacteriolysins, but high temperatures inhibit these immune reactions.

Leucocytosis.—This term indicates a transient increase in the number of leucocytes in the circulating blood. This is in contrast to the more permanent increases seen in the leucemias. The normal number of leucocytes varies within rather large limits; usually 5,000 to 10,000 per cubic millimeter of blood is considered normal but not infrequently larger numbers are encountered. The number varies with age, diet, posture, altitude and numerous other conditions. In early infancy the number may be as high as 20,000 per cubic millimeter or even more, diminishing during later infancy and reaching the adult figures at about the fifteenth year. Cummer suggests as standards for the proportion of the different types of leucocytes; polymorphonuclear neutrophils, 62–64 per cent., lymphocytes 22–28 per cent., large mononuclears and transitionals 7.5–10 per cent., polymorphonuclear eosinophiles 1–3 per cent., and polymorphonuclear basophiles (mast cells) 0.2–0.6 per cent. These estimates are only approximate and much wider ranges of the normal may be expected (Bunting). During the period of high counts in infancy and childhood, the lymphocyte proportion is much higher and the polymorphonuclear neutrophils much lower than in adult life. With or without increases in the total number of leucocytes, various pathological conditions may induce marked alterations in the proportion of the constituent cells. With a total

increase, these may be referred to according to the type cell showing most marked increase, as for example polymorphonuclear leucocytosis or eosinophilic leucocytosis. Without total increase, increases of constituent types are referred to as relative lymphocytosis, relative eosinophilia, etc.

Leucocytosis may be physiological or pathological. The physiological form includes that incident to digestion (Feinblatt), to pregnancy, and to muscular exercise. How these operate is not known, but the studies of Broun indicate that exercise stimulates the bone marrow and it may be that new leucocytes appear in the circulating blood as a part of this phenomenon. The pathological leucocytoses may be classified as posthemorrhagic, toxic, inflammatory, those of malignant tumors and a general group of cachectic and similar leucocytoses.

Posthemorrhagic leucocytosis begins to appear, according to Drinker, within ten minutes after severe hemorrhage and in cases of large hemorrhage may persist for as long as a week. Lee and Minot find less tendency to leucocytosis in chronic types of anemia. It seems probable that the immediate increase in leucocytes is apparent rather than real, and is due to a washing out of leucocytes from capillaries as the result of withdrawal of fluid from the tissues. The more lasting increase is perhaps a part of the general stimulation of bone marrow due to the hemorrhage. According to Bacon, Novy and Eppler, it may result from acute water shortage "with corresponding increase of body temperature and non-protein blood nitrogen."

The toxic leucocytoses include those due to drugs and those due to bacterial products. Certain chemicals such as the coal tar drugs, chlorates and carbon monoxide may produce leucocytosis through the destruction of erythrocytes or by a relative asphyxia, and the resultant stimulation of bone marrow. The action of narcosis may be asphyxial. Leucocytosis due to local application of such irritants as mustard oil, croton oil, and cantharidin may be attributed to products of the local inflammatory reaction. Various products of bacteria, including toxins, tuberculin, vaccines and protein extracts may produce leucocytosis, and this probably bears directly upon the problem of leucocytosis in infectious disease. Its mechanism is discussed under the inflammatory leucocytoses. Peptone, pus, and various tissue and organ extracts produce leucocytosis probably in the same way. Bacon, Novy and Eppler take the view that the activating substances are essentially the intermediate products of protein cleavage such as proteoses, peptones and polypeptids.

Inflammatory or infectious leucocytosis depends upon the severity of the infection and the reacting capacity of the body. Thus, fulminant infections may produce such immediate depression of the entire body as to lead to no leucocytosis. Other conditions may also produce decrease or absence of reaction. Within limits, the more severe the infection the greater the leucocytosis. Leucocytosis represents part of the general reaction, but it is difficult to say that any local inflammation associated with leucocytosis is necessarily to be regarded as an infectious disease in the narrower sense of the term. As a

general rule, infectious leucocytosis shows primarily a marked proportional increase in the polymorphonuclear neutrophiles, then a relative increase of lymphocytes and later of eosinophiles, but these latter increases do not blot out altogether the proportional increase of polymorphonuclear neutrophiles. Such leucocytoses show counts of about 15,000, 20,000 or more per cubic millimeter, of which 80 to 90 per cent. or more are polymorphonuclear neutrophiles.

Nearly all the infectious diseases are accompanied by leucocytosis, but the notable exceptions are typhoid fever (often showing a decrease in leucocytes and later a slight relative increase of lymphocytes), tuberculosis (except where secondary infection is present), measles, mumps, influenza, glanders and acute poliomyelitis. Malaria may show a leucocytosis at the time of the chill but otherwise either a normal or decreased leucocyte count.

Malignant tumors, of themselves, do not produce leucocytosis, except that lymphosarcoma may be accompanied by a relative lymphocytosis. Leucocytosis may result, however, from secondary changes in tumors such as infection or marked necrosis. Metastatic invasion of bone marrow may also stimulate a leucocytosis. The so-called cachectic leucocytosis of malignant tumors is probably to be explained by any of the secondary changes just mentioned, invasion of bone marrow or terminal infections such as pneumonia. Since many cases of most profound cachexia show no leucocytosis, it is highly probable that cachexia in itself has no such effect.

Agonal leucocytosis is that which often appears just before death. This may be due to slowing of the blood circulation so that the leucocytes accumulate in upper parts of the body or it may be due to terminal infections. It has also been supposed that the approach of death releases those forces which normally hold the immature blood cells in the bone marrow, thus permitting their entrance into the circulating blood; there is as yet no definite support for this hypothesis.

Origin of Leucocytosis.—The leucocytes are mature forms of cells; the polymorphonuclear cells do not undergo mitosis, the mononuclear cells only rarely, in the circulation. Therefore, leucocytosis is not due to multiplication of cells already in the blood. Virchow's hypothesis of stimulation of lymph nodes by products of the infectious process is vague and not conclusive; neither is any extension of this hypothesis to include bone marrow. With the discovery of ameboid motion and chemotaxis, it has been held that positively chemotactic substances gaining entrance to the blood attract cells from the bone marrow. Similarly, negative chemotaxis explains a decrease in circulating cells, or leucopenia. Typhoid bacilli appear to lead to endothelial hyperplasias rather than local or general leucocytosis; it therefore seems probable that they do not produce substances positively chemotactic for leucocytes, save perhaps when sensitized with immune serum (Gay). The products of tubercle bacilli are not positively chemotactic for leucocytes. These exceptions, therefore, do not controvert the general hypothesis. More recently, especially since emphasis has been placed on phagocytosis in the

defensive mechanisms of the body, leucocytosis has been regarded as part of the larger immune responses of the body to infection. As a part of this general immune reaction is possibly the production of defensive ferments by these cells. There is, however, little reason for believing that leucocytosis contributes to the formation of immune bodies or complement. This is a philosophic conception of leucocytosis which in no way contradicts, but simply enlarges, the hypothesis of chemotactic stimulus. It must be admitted, however, that this is a hypothesis and that the leucocytosis may be bound up in other factors incident to alterations of water balance in the body, to fever, and to protein cleavage products.

Metchnikoff indicated a certain degree of specificity of function of phagocytic cells when he differentiated micro- and macrophages. That there is, however, a qualitative difference in the type of cell in leucocytosis as the result of special demands for phagocytosis is open to question. Infestations by animal parasites, particularly the *trichinella spiralis*, may lead to an increase in the number of circulating eosinophiles, as is true also of certain inflammatory skin diseases, of which dermatitis herpetiformis is a striking example. The function of this eosinophilia is unknown. In infectious diseases of early childhood the leucocytosis may be predominantly lymphocytic, but what seems to be the same type of infection in other children and in adults is accompanied by a polymorphonuclear leucocytosis. Murphy points out that an increase of lymphocytes in the circulation of experimental animals appears to increase resistance to tuberculosis, but that this phenomenon occurs in man is doubtful. Hematologists have discovered certain important diagnostic features in the differential counts of the circulating leucocytes, but the reasons for these as well as the functions of the cell types concerned, are obscure.

Pathological Effects of Infection.—Most of the acute infectious diseases show lesions that are more or less characteristic. This is true of the skin lesions of the exanthemata. Pneumonia, typhoid fever, acute anterior poliomyelitis, epidemic meningitis and a host of others have identifying manifestations. They also exhibit lesions in common. Thus, a variable degree of acute hyperplasia of the lymphadenoid system is observed in many infections, as is also a more or less severe grade of secondary anemia. Of great importance, however, are the toxic effects of the disease upon parenchymatous viscera. These become apparent in the later asthenic stages of the disease rather than in the early sthenic stage. There is cloudy swelling and in more severe or long standing infections fatty degeneration; still greater severity may lead to focal necroses or to parenchymatous inflammations. Thus, cloudy swelling or more serious lesions of the myocardium may lead to low blood pressure and cardiac arrhythmias. Acute inflammations of the endocardium, particularly its valvular portions, may lead to death directly or give origin to crippling, chronic valve lesions. Pyemias may show abscesses in the myocardium. Fatty degeneration of the intima of the aorta is extremely common and more serious disease of arteries sometimes occurs, in rare in-

stances leading to such important lesions as aneurysms of small vessels. Veins are not uncommonly the seat of thrombophlebitis, especially as a sequel of typhoid fever. Serous membranes, more especially pericardium and pleura, often show acute inflammations which in case of recovery result in chronic fibrous adhesions. In the pericardium such adhesions may lead to serious disturbances of the heart. Voluntary muscles may apparently suffer from cloudy swelling and fatty degeneration. In typhoid fever, influenza and other infections, Zenker's hyaline necrosis occurs. Degenerative lesions of liver, pancreas and glands of the alimentary tract lead to digestive and nutritional disturbances. Cloudy swelling of kidneys may cause albuminuria and the appearance of hyaline casts. The process may become more severe and an acute nephritis develop. The nervous system may be affected by degenerative changes, but this is not common save in connection with diphtheria and those diseases where the nervous system is primarily involved.

The acute degenerative conditions are not only of import in the course of the disease but may be persistent for a long time after the disease has disappeared. Such sequels are more common with greater severity of the infection, and young individuals recover more readily than older ones. If acute parenchymatous inflammations develop, particularly in the kidney, they may become chronic and result in serious disability and ultimately in death. Acute infectious diseases are directly responsible for most of the chronic diseases of man, and represent the most common and most important group of conditions to be considered in any general study of etiology. This fact will become more and more apparent as the sections in special pathology are studied.

Special Types of Infections. Pyogenic Infections.—It must be recognized that the foregoing represents the briefest statement of some of the general principles of infectious disease. Many examples will be given in the section on special or systemic pathology, where infections of various systems and organs will be discussed. The pathology of numerous special infections must be studied in original communications and in special books on the subject. Our discussion of principles may be further elaborated by a few examples. Probably the simplest of these is infection by the staphylococcus aureus. Most of such infections originate in the skin or superficial orifices of the body, but staphylococci may accumulate in such crypts as hair follicles and multiply to such an extent as to invade through the skin. They may be introduced by scratching of such lesions as herpes and urticaria. As a rule, the first manifestation is a localized inflammation which may go on to the production of abscess. The inflammatory exudate operates through its fluid and the movements of the fluid, fibrin formation, and the activity of the leucocytes, to prevent further spread, and the subsequent growth of connective tissue may adequately wall off the infected area and lead to cicatrization and cure. The final walling off may not occur in the stage of abscess, so that a larger accumulation of pus, the phlegmon, may be produced. The local process may progress even further in the form of the so-called cellulitis, usually extending along fascial planes. If, however, resistance be low or virulence high a more

serious chain of events may ensue. In the virulent or widespread local inflammation, toxic bodies may be formed by the bacteria and by the tissues, which upon absorption produce general manifestations. This has been referred to as toxemia. The passage of the cocci into the lymphatic vessels may excite inflammation of the lymphatics between the site of infection and the nearest neighboring lymph nodes. Thus, lymphangitis is established, which may be followed by an acute hyperplastic lymphadenitis in the lymph node or nodes. Suppuration in the lymph tracts and nodes may result. This extension of the inflammation may also be favored by passage, into the lymph vessels or nodes, of phagocytes which have taken up bacteria but are unable to kill them. Bacteria may then be liberated and produce inflammation. Entrance to the blood stream may be determined by the bacteria passing through the lymphatic filters of the body or by direct invasion into small capillaries or venules as the local inflammation extends. If these capillaries and venules are not closed off by adequate protective thrombi, the phagocytes and free bacteria may gain access to the blood stream. Thus, there is established a septicemia, diagnosed both by the general manifestations and by obtaining cultures of the organism from the circulating blood. Clumps of bacteria may lodge in different organs either as the result of phagocytic activity on the part of lining endothelium, or because small clumps become stopped in tortuous capillaries or at the point of division of vessels. In these situations they may give rise to abscesses similar to those seen at the portal of entry (see Morris). The condition then becomes a pyemia. The gross and microscopical characters of these abscesses do not differ materially from those seen in the original focus, except that in the early stages they may have the form of infarcts. Such secondary or so-called metastatic abscesses are found particularly in the kidneys, spleen, heart, lungs, brain and other viscera but are distinctly unusual in the liver. Liver abscesses are more especially found when there is infection in the portal drainage area or in the gall bladder and ducts of the liver. This entire sequence of events may be checked at any period by the cellular and humoral resistance of the body. Thus, a toxemia does not necessarily lead to a septicemia nor a septicemia to a pyemia. After pyemia is established, however, the outcome is usually fatal, since such a manifestation is commonly accompanied by definite decreases in factors of resistance. The pathological effects are not limited simply to abscess formation. There are deleterious effects evident in the circulating blood, the bone marrow, and particularly in the parenchymatous viscera. Anemia is a common concomitant of such generalized infection. The parenchymatous viscera usually show cloudy swelling, which is particularly evident in cardiac and vascular musculature and in the cells of liver and kidney. If the intoxication be intense or of long duration, cloudy swelling is followed by fatty degeneration and in some instances by focal necroses.

Streptococcus infections follow much the same lines as do staphylococcus infections, but the local lesions due to streptococci, particularly the hemolytic variety, are likely to spread more rapidly and give rise to earlier toxemia than

is the case with staphylococci. Similarly, streptococci more readily gain access to the blood stream and produce more severe and more commonly fatal septicemias.

Much prominence has been given the studies of E. C. Rosenow on the elective localization of streptococci. The principle briefly stated is that streptococci, freshly isolated, tend to produce lesions in experimental animals similar to those of the patient. Thus, streptococci from endocarditis produce endocarditis in the rabbit, those from infected gall bladders produce gall bladder inflammation, and so on with streptococci from a wide variety of sources (see Billings). It has also been maintained that hidden and more or less latent foci of streptococci, more especially the green producing form (viridans), at tooth apices, in tonsils and other places are responsible for a wide variety of vague symptoms, particularly muscle pains, and for serious lesions such as endocarditis, nephritis, anemia, etc. The hypothesis is attractive, but confirmation is not convincing and contradiction has been offered by many well qualified workers. This statement has no bearing on the well established fact that points of lowered resistance may induce focal deposits of bacteria.

Suppuration may be produced by organisms other than the staphylococcus and streptococcus and follow the same general course. Colon bacilli, innocuous in the intestinal canal, may be extremely virulent in other situations, especially the peritoneum. Pneumococci, diphtheria bacilli, Friedlander's bacilli, and a host of others, under special conditions and situations, may be pyogenic.

Diphtheria.—This disease, due to the Klebs-Loeffler bacillus or bacillus diphtheriae, produces local and general symptoms. The local symptoms arise at the point of invasion of the specific organism and the general symptoms are due to its toxin. In so far as general manifestations are concerned, they are to be regarded as those of toxemia. The primary invasion is usually in the upper respiratory tract, particularly in the tonsils and fauces. Primary or secondary local invasion may occur in other situations such as skin, conjunctiva, etc. The lesions in the latter situations are likely to be limited and rarely produce serious toxemia. Involving tonsils and fauces, functional disturbance, in swallowing particularly, is usually due to the pain of inflammation. Extension into the nose may occur, or the disease may be primary in the nose, in which case nose breathing becomes difficult or impossible. Extension may also occur to the larynx, or the disease may be primary there, and obstruction to breathing is often serious or disastrous. The inflammation set up by the diphtheria bacillus is characteristically a fibrinous or fibrinopurulent inflammation. Destruction of the superficial epithelium is rapidly followed by fluid exudation and fibrin formation. The fibrin is deposited through a relatively small amount of the superficial part of the tissue, and is most massive as the so-called membrane or pseudomembrane on the surface. The fibrin mesh of the pseudomembrane and that of the tissues intercommunicate. Included in the exudate are desquamated epithelial cells, more or less degenerate or necrotic, a number of leucocytes, lymphocytes, diphtheria

bacilli, and other bacteria. In the early stages, this pseudomembrane appears as a smooth, well defined, creamy white or pale yellow material which, when detached, leaves a somewhat raw, slightly bleeding surface. As the disease progresses, the color may become distinctly yellow due to increasing infiltration

of leucocytes. The exudate may become more or less necrotic thus producing a shaggy or ragged surface, due to dropping out of necrotic material. The underlying tissues are hyperemic and show less dense but similar exudation. Extension along the bronchi may lead to bronchopneumonia which is usually distinctly fibrinous in character. Bronchopneumonia may also be produced by aspiration of small masses of exudate and bacteria. It appears probable that when the lung is involved, further extension may occur because of transmission along lymphatic tracts by a fibrinous lymphangitis. The older pathological anatomists applied the term diphtheritic inflammation to any type of inflammation which forms pseudomembrane on mucous surfaces. Thus, a similar membrane may be formed upon the surface of the intestine in bacillary dysentery. It seems wiser to apply to these other forms the term fibrinous inflammation, and to reserve the term diphtheritic inflammation solely for that due to the diphtheria bacillus. The term croupous inflammation has been applied to inflammation involving the respiratory tract from and including the trachea, downward. This term should be abandoned. The term croup is a clinical term indicating difficulty of respiration due to lesions within the larynx. This has no



Fig. 83—Laryngeal diphtheria. Note the fibrinous exudate on the surface, the large capillary spaces, edema and leucocyte infiltration of the underlying connective tissue.

direct bearing on the pathology of the condition, and as a rule diphtheritic croup and spasmodic croup can be distinguished.

The toxin of diphtheria is produced and absorbed from the local lesion. It is true that occasionally diphtheria bacilli gain entrance to the blood stream and probably elaborate toxins further in this situation. The severity of the

toxemia depends principally upon the capacity of the particular strain of diphtheria bacillus to produce toxin, the extent of the local lesion and the absorbing capacity of the surface involved. It is well known that the various strains and cultures of the diphtheria bacillus vary greatly in their ability to produce toxins (see Andrews, Bullock, et al.). As a general rule, the more extensive the local exudate the greater the intoxication, all other factors being equal. It seems highly probable that absorption from the larynx occurs less readily than from the tonsils and fauces. Exudate may be very extensive in the nasal cavities without producing as serious toxemia as is frequently seen in faucial diphtheria, but this is rather the result of low virulence than poor absorption. It seems probable that small amounts of antitoxin in the body, not sufficient to respond to the Schick test, may combat the toxin, and it is certain that as the disease progresses antitoxin is elaborated. It may be delayed, and in fact not be apparent in any way, in the presence of overwhelming doses of the toxin. Immunologically, the method of treatment is to introduce into the infected body antitoxin prepared in the body of the horse. Active immunization of man is practised by repeated injections of toxin-antitoxin mixture, a most valuable prophylactic measure. The pathological effects of the toxin are particularly upon the parenchymatous viscera, the adrenals and peripheral nerves. Thus, the heart and vascular muscle, the liver, kidneys and other parenchymatous organs show varying degrees of parenchymatous degeneration, from simple cloudy swelling to severe fatty degeneration and even necrosis. Circulatory deficiency is very common in man and in experimental animals. It has been thought that the circulatory failure is primarily vasomotor, but Marvin regards the evidence as inconclusive. The lesions of the heart and the studies of Edmunds and Cooper lend support to the conception that the myocardium is principally at fault. There is little good reason for believing that the transmission bundles of the heart are diseased. In addition to degenerations of the muscle, the myocardium may show acute interstitial inflammation. Occasionally acute endocarditis and pericarditis occur. Digestive disturbances are common and are believed to be due to parenchymatous degeneration of the glands. The liver particularly is likely to show severe cloudy swelling and even fatty degeneration. Focal necrosis of the liver is occasionally observed. The spleen and lymph nodes generally, including the Peyer's patches of the intestine, are likely to show varying degrees of acute hyperplasia. The kidneys are frequently involved

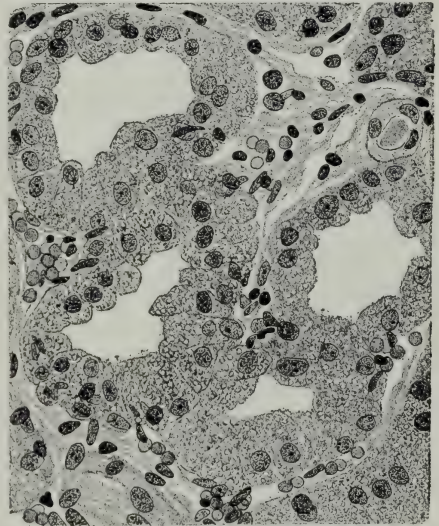


Fig. 84—Cloudy swelling and slight hydropic degeneration of the tubular epithelium of the kidney in diphtheria.

by cloudy swelling, which may evidence itself clinically by the presence of albuminuria and hyaline casts. It is not uncommon, however, for this change in the kidney to proceed further to an acute nephritis. The tubular epithelium may show in addition to cloudy swelling, fatty degeneration, hyaline droplet formation, and even necrosis; the interstitial tissues may be infiltrated by leucocytes, plasma cells and lymphoid cells. The glomerular capsules occasionally show proliferation of their epithelium, but more common is involvement of the glomerular tufts. In this situation, there may be swelling and

proliferation of capillary endothelium and frequently the formation of hyaline masses, or hyaline thrombi, within the capillaries. Lesions of peripheral nerves include degeneration of axis cylinders and of myelin sheath. These changes may be accompanied by a moderate infiltration of lymphoid cells and plasma cells, and may ultimately lead to fibrosis. As a result, paralysis occurs in palatal muscles and in other skeletal muscle; lesion of the vagus may lead to death from its influence on the heart. Skeletal muscle occasionally shows fatty degeneration and sometimes Zenker's hyaline necrosis. In experimental animals, hyperemia and hemorrhage of the adrenals occur; such lesions are common but not constant in man.

It will thus be seen that diphtheria in its more serious manifestations is principally a toxemia. Nevertheless, death may be due to local effects particularly in the case of laryngeal diphtheria.

Typhoid Fever.—This disease is due to infection by the bacillus of Eberth or the bacillus typhosus. It represents an infectious disease which is essentially a septicemia. Its local manifestations are especially prominent in the lymphoid apparatus of the abdominal cavity. Organisms are present in the blood stream very early in the disease, indeed as early as the third or fourth day after symptoms become



FIG. 85.—Hyperplasia and early ulceration of Peyer's patches in typhoid fever.

manifest, and cases have been reported in which the disease has run its entire course as a septicemia without local manifestations. The organisms are introduced into the body through the medium of food or drink taken by mouth, which either directly or indirectly are contaminated by feces of a victim of the disease. It is true that organisms may be found in the urine, but this is an infrequent source of infection as compared with that due to discharge in feces. After the disease has continued for two or three weeks the organisms disappear from the blood stream, local manifestations subside and general symptoms improve. The intoxication which accompanies the septicemia is probably due in large part to endotoxin liberated by the

death of organisms, but inasmuch as it is now known that bacillus paratyphosus B can elaborate an exotoxin, it seems possible that a similar exotoxin of bacillus typhosus may contribute in some part to the symptoms of true typhoid fever. The general symptoms include particularly varying degrees of prostration, fever, which reaches its maximum in the second or third week of the disease and gradually declines by lysis, and a very pale red macular eruption on the abdomen and in the axillæ and sometimes in other parts of the body. Diarrhea is frequent but not constant. The "pea soup" stools of the older writers probably depended more upon the diet given the patient than upon the disease itself.

The essential local lesions of typhoid fever are observed in the lymphoid apparatus of the abdominal cavity, including the agminated and solitary follicles of the intestinal canal, mesenteric and retroperitoneal lymph nodes and the spleen. The fundamentals of the course of events in these lymphoid aggregates are hyperemia, hyperplasia and necrosis. The hyperplasia of the spleen is observed at first as an enlargement which may reach a weight of 300 to 400 grams or more; it is a large, firm, red spleen, with a tense smooth transparent capsule. The organ cuts with decreased resistance and shows a slightly bulging, pink, fairly firm, moist cut surface. The Peyer's patches of the intestine enlarge in all diameters. They are sharply defined, somewhat pink, considerably elevated above the intestinal surface and superficially give a somewhat convoluted appearance suggesting the cortical surface of the brain of a small animal. The solitary follicles may show the same appearance except that they are not likely to be convoluted on the surface. Histologically, the enlargement of all these organs is found to be due partly to hyperemia, infiltration of plasma cells and occasional leucocytes, lymphoid hyperplasia, and partly to hyperplasia and multiplication of the endothelium of the lymphatic sinuses and of the pulp. The endothelial cells frequently show phagocytosis of nuclear fragments, of entire lymphocytes, of red cells, and of tissue detritus. Special staining will demonstrate typhoid bacilli, which are likely to be present in considerable numbers in the endothelial cells.



Fig. 86—Extensive ulceration of Peyer's patches in the ileocecal region in typhoid fever.

Following the stage of acute hyperplasia, necrosis appears. The necrosis is probably due to interference with free flow of nutritive fluid, due to the general hyperplasia and possibly in part due to substances elaborated by the organism. In the spleen and lymph nodes the necrosis is not usually visible

grossly, except that these organs become distinctly softened. Microscopically, however, minute foci of necrosis may be demonstrated. The same process occurs in the Peyer's patches, but inasmuch as these are upon a body surface, namely the surface of the intestinal canal, necrotic material is likely to slough out of the Peyer's patch leaving an ulcer. At first the ulceration appears as multiple small ulcers in the surface of the Peyer's patch; the ulcers subsequently fuse together so as to be coextensive with the patch. The edges are likely to be somewhat undermined and the base rough and often stained by the intestinal contents. In the uncomplicated cases the necrotic areas of the spleen and lymph nodes are removed in the usual way. The Peyer's patch becomes covered with surface epithelium under which is cicatricial tissue due to organization. In young individuals there is undoubtedly some regeneration of the lymphoid structures, but the glandular epithelium does not regenerate. There is no attempt made in this discussion to correlate the anatomical changes

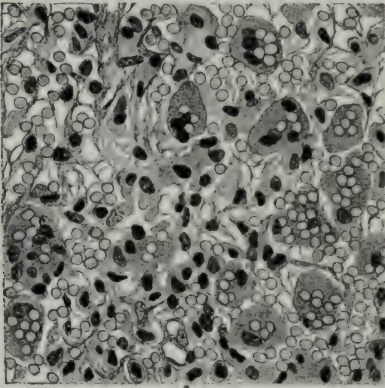


Fig. 87—Endothelial phagocytes of the spleen in typhoid fever.

with the stages of the disease in terms of weeks. No such correlation is accurately possible. In the same case, for example, one frequently sees in the upper part of the ileum simple hyperplasia whereas in the lower ileum necrosis may be well advanced.

The local lesions in the intestinal tract may show serious complicating features. When necrosis occurs in the Peyer's patches and material drops into the intestinal canal, a raw surface is exposed which is susceptible to secondary infection from the intestinal contents. Thus, the ulcer in its later stages represents not simply a necrotic ulcer, but because of the secondary infection is likely

to extend more deeply into the intestinal wall. It may progress as far as the peritoneal coat. As the ulceration extends, there is in the margin a definite inflammatory reaction, and as the peritoneal coat becomes involved, inflammation appears on the peritoneal surface, particularly in the form of a fibrin deposit. The further extensions of the ulcer determine perforation of the intestinal wall with liberation of the intestinal contents and contained bacteria into the peritoneal cavity. If the perforation has progressed slowly, the preceding deposits on the peritoneal surface may bring about adhesion to neighboring coils of gut or to the abdominal wall, so that when the perforation occurs, it may go into a small cavity entirely surrounded by fibrin and fibrinous adhesions. Often, however, this protective fibrinous adhesion does not occur or is torn by distention and movement of the gut, and a general peritonitis ensues. In the ordinary course of events, when an ulcer occurs in any situation, the inflammatory reaction in the margin includes a protective thrombosis of any blood vessels which happen to be in the path of extension. If, however, the ulceration be extremely rapid, this thrombosis may not be

sufficient to protect against the pressure in the blood vessels, the thrombi may be expelled and hemorrhage occurs. In the intestinal wall a further danger comes from intestinal movement and particularly from distention by gas which may be sufficient to dislodge thrombi and thereby lead to hemorrhage into the lumen of the gut. The two important complications of typhoid fever referable to the intestines, are perforation and hemorrhage. The hemorrhage may lead to severe secondary anemia or even to death.

As in all serious infectious diseases, typhoid fever also is likely to be accompanied by cloudy swelling of parenchymatous organs and in the more

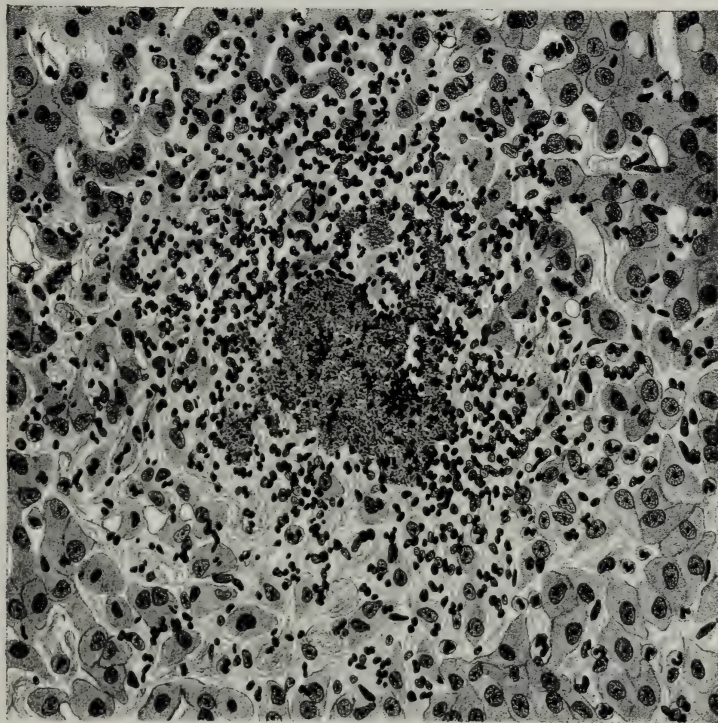


FIG. 88—Early focal necrosis of the liver in typhoid fever, showing infiltration of endothelial cells and an unusual number of leucocytes.

severe cases, fatty degeneration. Various organs may be involved in the course of typhoid fever with lesions more or less characteristic of the disease. In the alimentary canal as a whole, the mouth and pharynx may be the seat of mild inflammation which occasionally goes on to ulceration and sometimes membrane formation. The esophagus is sometimes ulcerated immediately posterior to the larynx. The stomach may show a mild catarrh, and in extremely rare cases the lymphoid follicles of the stomach are involved similarly to those of the intestine and may go on to ulceration. A general catarrhal inflammation of the ileum sometimes occurs, particularly if there be severe secondary infection of the ulcers. This may be accompanied by pseudomembrane formation and sometimes the gut becomes gangrenous. In the respiratory system, enlargement and even ulceration of the tonsils may be encountered. A low

grade inflammation of the larynx is not rare and occasionally may show pseudomembrane formation with serious disturbance of respiration. Ulceration may also appear in this situation. A common accompaniment of typhoid fever is passive hyperemia of the dependent parts of the lungs. A low grade catarrhal bronchitis is fairly frequent and this, in association with the passive hyperemia and edema, may finally result in a bronchopneumonia. The association of lobar pneumonia with typhoid fever is not rare. Pleurisy may occur and occasionally empyema is observed.

The circulatory system shows important disturbances; general blood pressure is low and diastolic pulse is almost constant in typhoid fever.

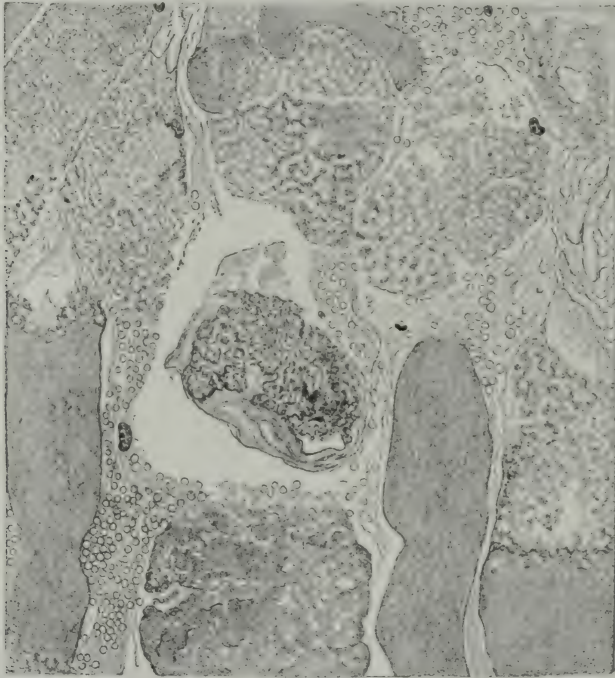


Fig. 89—Zenker's hyaline necrosis of skeletal muscle in typhoid fever.

Cardiac muscle usually shows cloudy swelling, may show fatty degeneration and occasionally shows hyaline necrosis. Inflammations of the pericardium and endocardium may occur. Not uncommon is thrombosis of the veins, particularly the iliac and femoral. In the genito-urinary system, aside from cloudy swelling of the kidney, occasional cases of acute nephritis are encountered. The bladder may be the seat of catarrhal or pseudomembranous inflammation. Orchitis and epididymitis occur rarely. In the nervous system degenerative changes are encountered in the ganglion cells and thrombosis of venous sinuses may occur. Typhoid meningitis has been reported in several instances. In the bone, low grade periostitis sometimes occurs and in rare instances actual suppurative periostitis. In the muscles, particularly the recti abdominis, a common change is Zenker's hyaline necrosis.

Focal necrosis of the liver is more common in typhoid fever than in any other disease. Grossly the necrosis is only rarely visible. Microscopically, the areas of necrosis are irregularly distributed and occupy only a small part of the lobule. In the section they are generally circular, with complete disappearance of cord cells, and in their place a mass of endothelial cells with



FIG. 90—Acute hyperplasia of mesenteric lymph nodes in typhoid fever.

which there may be a few lymphoid cells and an occasional polymorphonuclear leucocyte. The origin of these lesions has been discussed in the chapter on necrosis and somatic death.

The survival of an attack of typhoid fever usually, but not invariably, confers a lasting immunity. The immunity to paratyphoid fever conferred by an attack of typhoid fever is probably not as great as with the homologous

disease. Immunity is further indicated by the elaboration of demonstrable immune bodies; low titre agglutinins appear toward the end of the first week of typhoid fever, reach their maximum in the third week, and then gradually decline, but persist over many years. Precipitins, opsonins and complement fixing bodies also appear. Skin reactions may also be demonstrated by application of typhoid antigen. It is noteworthy that agglutinins do not attain the same high titre as the result of the disease as following inoculation with typhoid vaccine.

Paratyphoid Fevers.—In principle these follow the same general rules as laid down for typhoid fever. Whereas the course of typhoid fever runs over a period of three or four weeks before convalescence sets in, in the case of paratyphoid A the course may be shorter, and in the case of paratyphoid B considerably longer. In general, however, these types are not so severe as is typhoid fever. The pathological lesions and the immunological reactions are much the same. Certain forms of the typhoid bacillus not included in these three categories have been described and are generally grouped under the comprehensive heading of paratyphoid C.

Summary.—In the foregoing material, emphasis has been laid upon principles which may be widely applied in the consideration of any infectious disease. The etiological agent should be considered, in so far as it can be determined, in reference to predisposing causes, direct local and general effects, distribution, transfer, invasion and preventive measures. The infected body should be considered as to special conditions of exposure, special susceptibilities, resistance, physiological, anatomical and immune reactions both local and general, morbid anatomical and functional disturbances, and sequels. Numerous features are common to a wide variety of infectious diseases, but in each instance the special features must be considered. Thus pyogenic, typhoid, and diphtheria infections exhibit fever, cloudy swelling, fatty degeneration and diffuse inflammations of parenchymatous viscera in common with all toxic infections, but the pyogenic infections have special features in the abscesses, typhoid in the local lesions of the intestine, etc., and diphtheria in a particular type of local inflammation, etc. Many of the granulomatous infectious diseases show only slight general effects but have more or less characteristic lesions. Because of this they are given special study. Rabies, acute anterior poliomyelitis, epidemic encephalitis and tetanus are considered in the section on nervous diseases. Pneumonia, influenza, etc. are considered in the chapter on respiratory tract. The exanthemata are completely discussed in texts on dermatology, and only their general effects and sequels can be considered in our compass. Dysentery and the enteric fevers are discussed in the chapter on gastro-intestinal canal.

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CHAPTER X

THE INFECTIOUS GRANULOMATA

- DUE TO BACTERIA.
 - TUBERCULOSIS.
 - LEPROSY.
 - GLANDERS.
 - RHINOSCLEROMA.
- DUE TO SPIROCHETAL ORGANISMS.
 - SYPHILIS.
 - YAWS.
- DUE TO HIGHER BACTERIA.
 - ACTINOMYCOSIS.
 - MYCETOMA (MADURA FOOT).
 - STREPTOTHRICOSIS.
- DUE TO HIGHER VEGETABLE PARASITES (YEASTS AND MOULDS).
 - BLASTOMYCOSIS.
 - COCCIDIOIDAL GRANULOMA.
 - TORULA INFECTIONS.
 - SPOROTRICHOSIS.
 - ASPERGILLOSIS.
- WITHOUT CLEARLY PROVEN CAUSE.
 - HODGKIN'S DISEASE.
 - MYCOSIS FUNGOIDES.
 - GRANULOMA INGUINALE.

Introduction.—The infectious granulomata are often referred to also as specific inflammations. The latter conception is not correct since all these conditions are manifestations of infectious disease and represent more than local reactions to injury. Neither is the term granuloma fully acceptable since the lesion is not that of tumor. Nevertheless, all these diseases show at some period, or in some forms, a tissue proliferation resembling more or less closely inflammatory granulation tissue. Most of them are caused by known specific organisms, which in man and in experimental animals produce the special type of lesion. From the viewpoint of the student of infectious diseases there is little reason for establishing a special group, since the granulomata exhibit phenomena common to all the infectious diseases. Neither is there ground for special grouping in the fact that the lesions are in a general way of specific character, since other infectious diseases, such as typhoid fever, also produce characteristic anatomical changes. From the viewpoint of the pathological anatomist and histologist, however, the lesions have much in common and separate discussion of them is justifiable. They are therefore studied in this chapter on the basis of their morphology. Groups are arranged so as to emphasize the common infectious origin, and in the discussion of the processes their systemic effects are not overlooked. The infectious granulomata must be regarded as specific infectious diseases in the course of which nodules or granules are produced, and which have a certain but variable resemblance to inflammatory granulation tissue. This resemblance may be gross or microscopic or both but in certain instances is not so close as to be impressive. It is possible, as the various diseases are studied, to see that certain types closely

resemble granulation tissue but that in certain others, the resemblance is remote and grouping with the granulomata only justified on the basis of comparison, not directly with the simple inflammatory granulation, but with other granulomata. The tubercle of tuberculosis and the gumma of syphilis are to be regarded as type granulomatous lesions, and although these nodules usually exhibit only those cells common to granulation tissue, yet other diseases such as glanders and actinomycosis may show deviation from this conception in their cell picture. Furthermore, the organisms which induce the formation of granuloma may, under various circumstances of virulence, dosage, resistance or allergic alteration of reaction capacity, lead to the formation of lesions with little or no resemblance to granulation. For example, the tubercle bacillus, although it usually induces tubercle formation may also produce marked acute inflammatory reaction.

Rhinoscleroma is grouped with the granulomata due to bacteria, because although there is some question as to the organism, the bacillus rhinoscleromatis is generally regarded as the cause. On the other hand, the bacterial nature of Hodgkin's disease is less clearly proven and less widely accepted, and it is therefore grouped with the granulomata of unknown origin.

TUBERCULOSIS

Introduction.—Tuberculosis is an infectious disease caused by the tubercle bacillus. The manifest lesion, or lesions, is variable and depends for its structure upon numerous factors, such as the number and virulence of the organisms, point of entry, dissemination in the body and the resistance of the host. The most characteristic lesion is the tubercle, but this varies in its constitution depending upon some of the factors enumerated. In addition the tubercle bacillus may excite diffuse acute inflammatory reaction, usually with, but sometimes without, special characters. Functional disturbances may be the result of local destruction of tissues or the products of the tubercle bacillus or both. The disease has existed since prehistoric times, but its characteristics were really first determined by the work of Reid and of Baillie in the latter part of the eighteenth century. Villemin, in 1865, demonstrated the unity of the various tuberculous processes and proved the inoculability of the disease, and in 1882 Robert Koch discovered the tubercle bacillus.

The Tubercle Bacillus.—The bacillus tuberculosis is an aerobic, non-motile, non-spore bearing, gram positive rod, of somewhat variable size but measuring about 1.5 to 3.5 by 0.3 micra, i.e., approximating in length about one-fourth the diameter of a human erythrocyte. The organism is acid-fast, and when stained shows beading. It is said to be made up of delicate skeleton like membrane, an enclosing fuchsinophile sheath and an internal gram positive substance. The organisms grow slowly but readily upon culture media, such as blood serum, glycerin agar, glycerin broth, egg, potato and numerous synthetic media. The colonies at the end of about eight days are small, discrete and dry. They coalesce to form a rough, shaggy growth on surfaces, which does not extend into the water of condensation. Surface pellicles appear on fluid media similar to the growth on solid media. The culture mass takes fat stains, but the individual organisms do not. Numerous studies of the chemical constitution of the organisms have been made, as reviewed by Calmette and by Wells, DeWitt and Long. These may aid in further understanding of the disease and the development of an adequate chemotherapy. The resistance to acid decolorization has been attributed to the fat and lipid content of the fatty or waxy envelope, but according to Wells this

character is dependent upon the physical integrity of the envelope, rather than upon the capacity of the fats and lipoids to retain the dye.

The organism is regarded as a bacillus or bacterium but differences of environment, both *in vivo* and *in vitro*, may induce alterations in length and breadth. Furthermore, branching forms have been observed in culture, sometimes ramified and with terminal swellings or bulbs. Branching forms may appear in resistant animals but are only rarely seen in human sputum. Calmette states that in fresh, young cultures the organisms may show cilia at the poles and exhibit genuine motility. Chemically the organism has both animal and vegetable features (Long).

Three varieties are well recognized, the human, bovine and avian. That these represent true and inherent differences is open to question. Certain careful studies indicate that repeated animal inoculations may transform bovine into human forms, and studies of numerous cultures show border line forms, which are difficult to classify. Many now hold that the differences in form, growth, and virulence which distinguish the types are acquired as the result of habitual growth in the different animal species and are not permanently inherent in the organisms. Although avian infections have been reported in man, the really important forms for man are first and foremost the human type and second the bovine type. It is usually stated that the human type is long and narrow, and the bovine type is short and thick but this differentiation is of no value. Thanks to the work of Theobald Smith, of Park and Krumwiede, and others a more rational differentiation is possible. Smith pointed out in 1903 that the human form rapidly and permanently acidifies glycerol broth, whereas the bovine form only slightly acidifies the medium. Park, following the work of Moeller and of Beck, found that the addition of glycerol to the Dorset egg medium aids the growth of the human form and retards the bovine form. On the other hand, the non-glycerolated egg provides much superior growth of the bovine form. Park and Krumwiede use this method and in addition inject four rabbits intravenously, two with 0.001 gram culture each, and two with 0.00001 gram. Bovine bacilli are rapidly generalized and usually kill the animals, whereas the human bacilli lead to only slight and slowly progressing disease. The difference in dosage aids in evaluating virulence for the animals. Guinea pigs are somewhat more susceptible to human than to bovine bacilli but the difference is likely to be slight and not of diagnostic import. Numerous other methods of differentiation have been devised; the hygienic significance of proper differentiation is so great that too much refinement cannot be attained.

Tubercle bacilli are resistant to desiccation, particularly in the dark, and survive putrefaction in the tuberculous corpse over several years; they resist extremely low temperatures. They are destroyed rapidly by sunlight and ultraviolet rays, less rapidly by diffuse daylight; they are destroyed by heat, particularly moist heat, ozone, and the disinfectant chemicals.

The usual laboratory diagnosis of tuberculosis depends upon staining the organisms by the Ziehl-Neelsen technique or the production of characteristic lesions in guinea pigs. Two healthy animals are selected and the material injected either intraperitoneally or subcutaneously in the lower belly wall or hind leg. In the former, peritoneal and lymph node (especially mediastinal) tuberculosis may be demonstrated in three or four weeks, not infrequently accompanied by involvement of spleen, lungs and other organs. Subcutaneous inoculations may be followed in two weeks or more by tuberculosis of the regional lymph nodes.

Modes of Entry of the Tubercle Bacillus.—The tubercle bacillus can gain access to the body through any of the surfaces which are connected with the exterior, but as a matter of practical fact, the important modes of entry are through the respiratory tract and the alimentary canal. It is doubtful that tubercle bacilli ever gain access to the body through the genito-urinary canal, except in those rare instances where open lesions of the external genitalia permit transmission by sexual contact. Implantations occur in the skin through accidental infection, such as pricks with infected syringe needles or cuts with infected instruments.

A discussion of infection with the tubercle bacillus must consider modes of dissemination, primary infection, reinfection or superinfection, and transport within the body. The more recent studies of tuberculosis leave no room for doubt that most primary infections occur in childhood. By the end of the sixth year of life from 50 to 60 per cent. of all children are infected; at fifteen years of age 75 per cent. or more are victims, and it is generally conceded that in adult life 90 per cent. or more show evidence of having been infected at

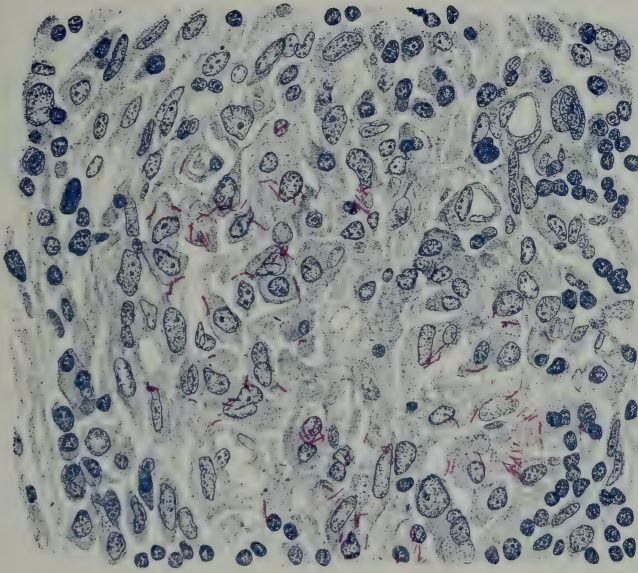
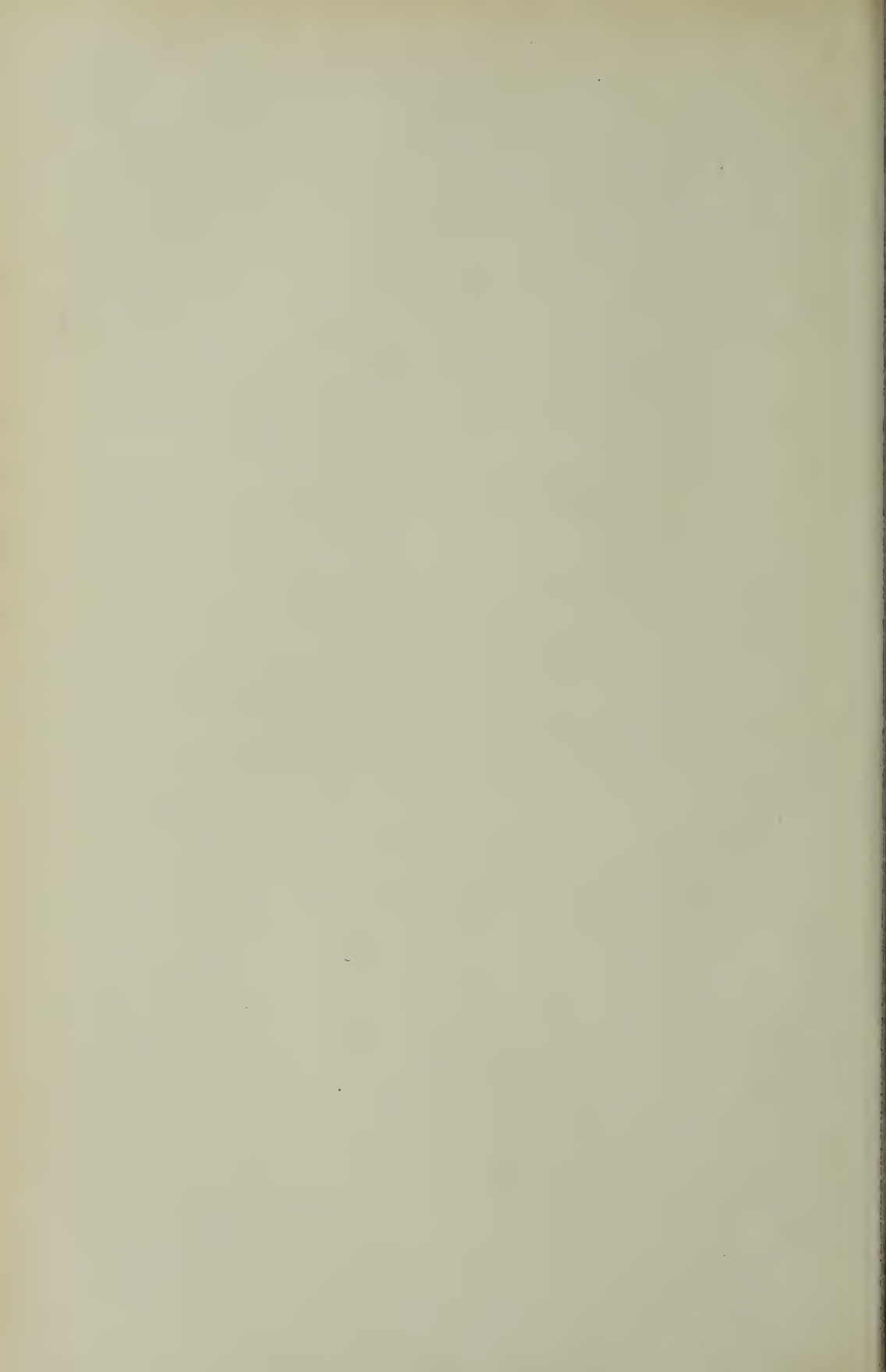


PLATE VIII—Microscopic drawing of tubercle bacilli (carbol-fuchsin) in an early tubercle. Bacilli are found in and between endothelial cells. Lymphoid cells and plasma cells are found in the margins.



some time. Various hypotheses are advanced concerning modes of dissemination of organisms, and there is little doubt that all may have a basis in fact. The most frequent origin is undoubtedly infected human sputum, but infected cow's milk is also an important source. Dusts containing dried sputum may be inhaled; droplets forcibly exhaled in coughing, sneezing, etc., may be inhaled in the moist state; these presumably lead to tuberculosis of the lungs or mediastinal lymph nodes. Tuberculous cow's milk may upon ingestion lead to intestinal or mesenteric lymph node tuberculosis and possibly by transfer from the abdomen give rise to pulmonary tuberculosis. The infection

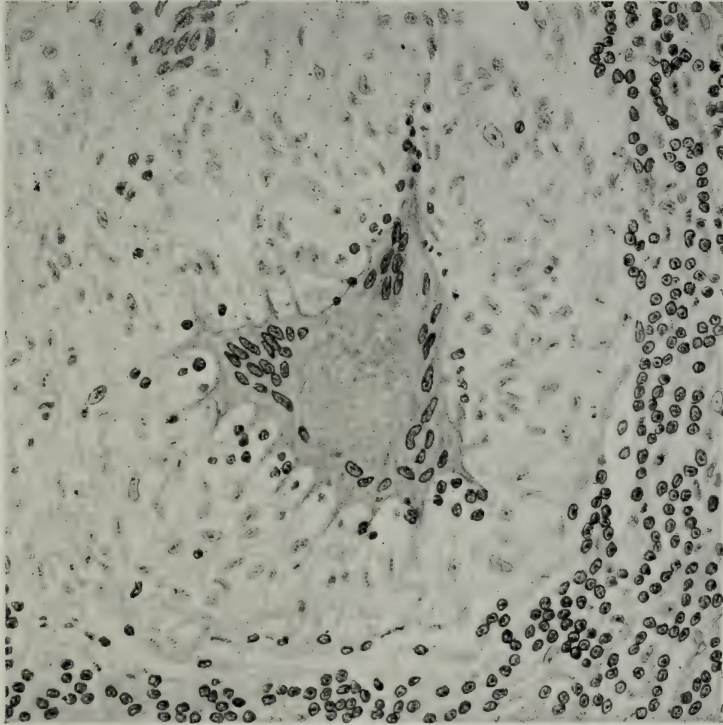


Fig. 91—Giant cell in center of miliary tubercle, showing processes of cytoplasm.

is indoor rather than outdoor. The greatest incidence of clinical tuberculosis in childhood is in the cervical lymph nodes. Krause strongly supports the hypothesis that although the methods outlined above are important, nevertheless, the commonest mode of transfer is through more or less fresh sputum on floors, furniture, tracked into the house on boots, etc., which contaminates the infants' or children's hands and is conveyed to the mouth. It may thence infect the upper respiratory passages and cervical nodes, may gain access to lower respiratory tract, or be swallowed and lead to intestinal infection.

In order to produce infection the organisms must pass through the mucous covering of the usual portals of entry. Introduced in small numbers, the bacilli may produce no local lesion whatever. This has been shown repeatedly

by experimental inoculation through the intestinal canal, and is commonly observed pathologically in deep lesions of the tonsils and of the cervical lymph nodes, as well as in tuberculosis of the mediastinal and mesenteric nodes without demonstrable lesion in the lungs or intestine. There has been much discussion concerning the reciprocal relationship between primary pulmonary tubercles and tubercles in the mediastinal lymph nodes. It has been thought that the tubercle bacilli pass through the lung and set up disease in the neighboring lymph nodes; retrograde dissemination through the lymph vessels then establishes disease in the lung. The work of Kuss, of Albrecht and of Ghon gives convincing pathological evidence in support of the statement that in nearly all instances the lesion is primary in the lung and secondary in the tracheobronchial or bronchopulmonary lymph nodes. Ghon, for example, was able to exclude a primary, pulmonary lesion in only two of 170 cases. The

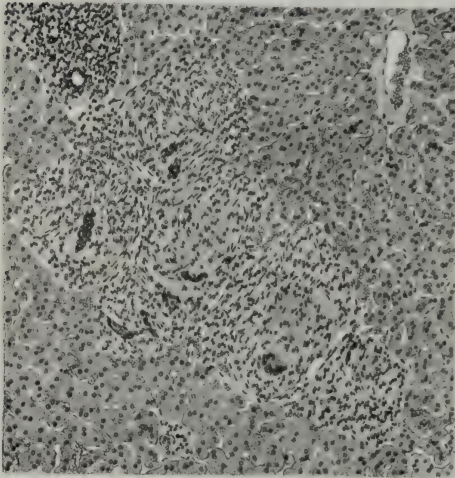


Fig. 92—Miliary tubercles of liver in early stage of coalescence.

conception is also supported by the admirable work of Opie with adult lungs. We may therefore say that, gaining entrance to the tissues, the organisms may excite a local reaction and either with or without lesion be transmitted to the regional lymph nodes; this is natural in view of the intimate connection of the tissue spaces with the lymphatics. It is therefore probably incorrect to assume that the primary pulmonary tubercle arises within the air containing infundibulum; it is much more likely that the lesion arises within the wall of this structure, or in neighboring lymphatics. Similarly, lesions in the

intestine are within the lymphoid structures of the submucosa rather than upon the mucous surfaces. Accidental inoculation of the skin is followed by tubercle formation in the corium or subcutaneous tissue rather than in the epiderm.

Civilized man is almost uniformly the victim of tuberculization by the time adult life is reached. The first infection usually takes place in childhood or even late infancy. This primary lesion may spread and cause death, it may rarely become a chronic progressive process, or as is most often the case it becomes encapsulated and calcified. Active tuberculosis in childhood is preponderantly in lymph nodes, bones and joints and meninges, whereas pulmonary tuberculosis is principally a disease of adult life. Opie states that it is "seldom if ever possible to demonstrate by anatomical examination that apical tuberculosis of adults has spread from a focal lesion of childhood." Much evidence has accumulated to favor the view that adult tuberculosis is a reinfection or superinfection.

The type of tubercle bacillus concerned varies in percentage with the time

of life. The human type, however, is the most frequent invader of man throughout his life. In childhood the incidence of bovine type of bacilli is distinctly higher than in adult life. Thus, tuberculous cervical lymphadenitis of childhood is frequently due to bovine bacilli, but the majority of the cases are due to the human type. Park and Krumwiede showed that from 6 to 10 per cent. of the deaths from tuberculosis in childhood can be ascribed to the bovine bacillus but that in adult life this organism is negligible as a cause of the disease. Cobbett, however, believes that the bovine bacillus may be responsible for a small but significant percentage of adult cases.

Types of Lesion.—Infection by the tubercle bacillus may lead to the development of the tubercle, or, much less frequently, may lead to the development of an acute inflammatory reaction, usually with some special characters. Chronic tuberculous inflammation is attendant upon prolonged tuberculous infection. The tubercle is the result of local proliferation and infiltration, whereas other tuberculous lesions are exudative. The tubercle is essentially interstitial in situation, whereas acute tuberculous inflammation affects surfaces such as pulmonary alveolar surfaces, and serous membranes such as pleura, meninges and joints. This does not, however, exclude the possibility of tubercle formation upon such surfaces. The tubercle is a lesion which histologically is extremely characteristic and grossly is, as a rule, easily distinguishable. The simple discrete tubercle is composed of a central mass of large oval or elongated cells with fairly large vesicular nuclei. These are called the endothelioid or epithelioid cells. The studies of Foot and others indicate that these may properly be called endothelial cells. Surrounding these is a mass of lymphocytes. As this lesion develops, the tissues occupied are destroyed, so that within the lesion no remnant of original tissue is likely to be found. Secondary changes occur very early in the course of the process. Endothelial cells often fuse together to form the so-called giant cells of Langhans, which when fully developed are large multinucleated cells with a finely granular cytoplasm. The outline is frequently irregular because of the projection of small cytoplasmic processes, which may extend as minute fibrils out into the surrounding tubercle. The nuclei are somewhat more deeply chromatic than in the original endothelial cell. The nuclei are oval and frequently arranged in a circle around the margin

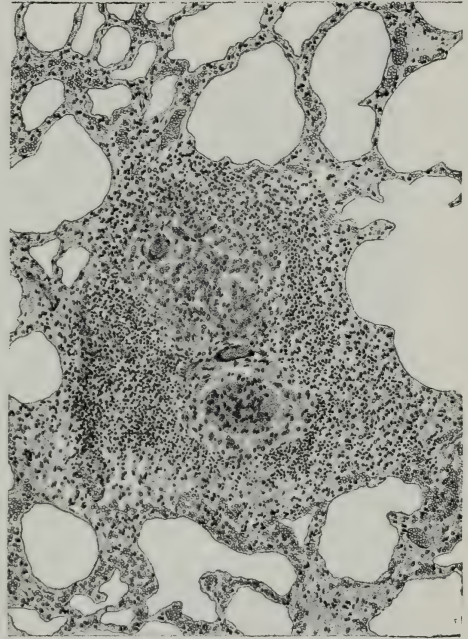


Fig. 93—Miliary tubercles of lung with several giant cells.

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of the cell with their long axes in radial position. Sometimes the cell is elongated in character and shows nuclei only at the poles. If the line of section of the cell include only the pole, then the nuclei may appear to be centrally disposed in the cell. Special staining frequently demonstrates tubercle bacilli within the cytoplasm of the giant cell. Not infrequently the center of the cell is the seat of caseous necrosis.

Caseous necrosis of the center appears early in the course of the tubercle and involves particularly the endothelial cells and giant cells. Histologically, the caseation shows simply a granular necrotic mass. As the process continues and the tubercle enlarges the central caseation also increases in amount. Of great importance is the fact that in the construction of the tubercle, blood

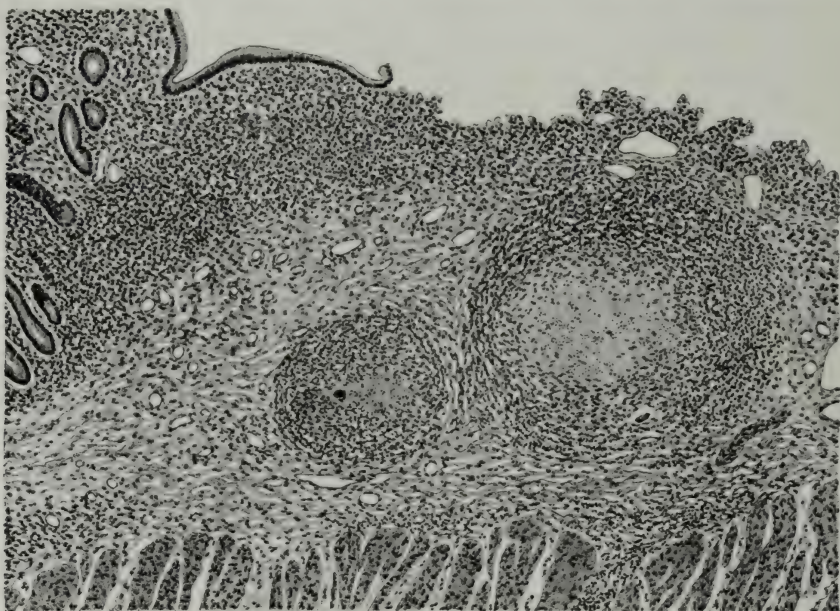


Fig. 94—Miliary tubercles of intestine, underlying an ulcer. Caseation is advanced.

vessels do not play a part; the lesion is avascular. The central necrosis in the tubercle is in part the result of the lack of vascularization, and in part perhaps of cellular enzymes, although these have not been satisfactorily demonstrated (Reed). The caseous material and the wall of the tubercle are, as has been shown by Caldwell and others, richer in alcohol-ether soluble substance than is normal tissue. This soluble material consists largely of cholesterol, phospholipins and unsaturated fatty acids and their soaps. The protein content is chiefly in the form of coagulated protein which undergoes little or no digestion (see Wells, De Witt and Long). Caseous areas tend to remain caseous or to become even more solid. Ordinarily, they show no disposition toward softening or liquefaction and this is believed by Jobling and Petersen to be due to the presence of soaps of fatty acids which have a marked antitryptic effect, and therefore inhibit the action of autolytic ferments. There appear

to be no soluble chemical substances in the tubercle which serve to attract leucocytes. If, however, secondary infection by other organisms occurs, positively chemotactic substances appear and leucocytes enter. When this occurs the antitryptic effect of the soaps of fatty acids is insufficient to prevent the action of proteolytic ferments and the area softens and liquefies. In summary it may be said that the essential histological elements of the tubercle are the endothelial cells and the lymphocytes. The usual picture, however, is that of central caseous necrosis surrounded by one or more giant cells and many endothelial cells, these in turn surrounded by a zone of lymphocytes.

The tubercle may increase in size either by growth of the original tubercle or by the formation of secondary or daughter tubercles. It is believed that the

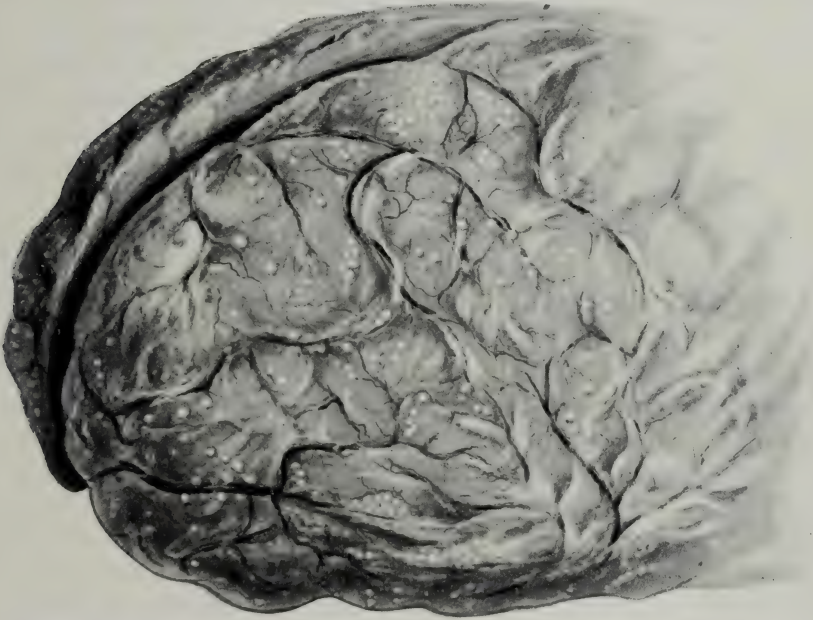


Fig. 95—Miliary tubercles in pia-arachnoid of the cerebrum.

migration of phagocytic endothelial cells containing live bacilli, or the transmission of bacilli in the flow of tissue juices serves to implant a few organisms in the immediate neighborhood. These lead to the production of secondary tubercles. As these enlarge they join with the original mass to produce a more rapid enlargement. This process of secondary tubercle formation and successive enlargement of the original mass may go on to the production of large solitary tubercles, such as are found in the brain or in the liver where diameters of 1, 2 or 3 cm. are not uncommon. At any stage during the progress of the tuberculous lesion, resistance may become sufficient to prevent further spread. When this occurs, the reaction is no longer limited to the endothelium and the lymphoid cells, but is participated in by connective tissue elements so that outside the layer of lymphocytes and involving it, to a certain degree, proliferating connective tissue is found. This may be of the type of granulation

tissue and is fairly well vascularized. In the majority of instances, however, the growth of connective tissue is slow and little vascular participation is observed. By the growth of this connective tissue the entire area may be completely encapsulated. After encapsulation has occurred, the lesion may remain quiescent throughout life or may exhibit renewed activity due to conditions which are discussed in the section on immunity to tuberculosis.

Histogenesis of the Tubercle.—The histology of the lesion was first described by Virchow and the true types of cell comprising the lesion, the giant cell, the endothelial cell and the lymphoid cell were differentiated by Schueppel. Since that time numerous studies and hypotheses have been contributed concerning the growth and development of the tubercle. Until methods were devised for differentiating the endothelial cell on a satisfactory basis, studies were necessarily very largely a matter of personal opinion. The recent studies of Evans, Bowman, and Winternitz and of Foot have thrown great light on this problem. By the use of intra-vitam dyes they have been able to demonstrate the origin of the large mononuclear cells in the tubercle. The primary lodgment of tubercle bacilli, notably in the liver of experimental animals, may be followed immediately by a certain amount of heaping up of leucocytes and the formation of a small amount of fibrin. This phenomenon is only rarely, but sometimes, observed in early human tubercles. These cells, however, do not form a constant or permanent part of the picture of the tubercle. Krause believes that the response to the infection depends, at least in part, upon whether the infection be primary or secondary. If primary, the response is confined to endothelial cells and lymphocytes. If superinfection or dissemination occur, the response may be more distinctly inflammatory in type as the result of an alteration in reacting capacity of the body, due to the presence of the primary infection. This alteration of reactive capacity is regarded as an allergic manifestation. The endothelial cells originate by proliferation of preëxisting endothelium of small blood vessels or lymphatic vessels at the site of the lesion, or as Foot has indicated, they may migrate from vessels slightly removed from the point of lodgment of the bacilli. There is no doubt that the giant cell takes its origin from the proliferating endothelium. Evans, Bowman, and Winternitz are of the opinion that formation of the giant cell depends in part upon the multiplication of nuclei by mitotic division, but that further growth may depend upon fusion with other mononuclear or multinuclear cells. The subsequent increase in nuclei may result from within the giant cell. Mallory is of the opinion that the giant cell of tuberculosis is the result of fusion of the endothelial cells, and this view is confirmed by experimental work of Foot. Foot's later work indicates that giant cells can exhibit mitotic activity. The lymphocytes appear somewhat later in the course of development of the lesion, but no explanation has as yet been offered for their appearance and no demonstration as to their mode of origin has been made. Foot is of the opinion that inasmuch as many of the endothelial cells migrate to the point of irritation, even from the circulating blood, the lesion may be considered as exudative in character. Lewis, Willis

and Lewis find that they closely resemble the large mononuclear or monocyte of the circulating blood. Nevertheless, multiplication of endothelial cells appears in situ. Foot has also shown that endothelial cells which have taken up tubercle bacilli, may migrate to neighboring lymphatics and lymph nodes and thus be a source of dissemination of the disease.

Lesions Other than the Tubercle.—The implantation of tubercle bacilli does not invariably lead to the development of the tubercle. Especially when implanted upon serous membranes such as the meninges, the pleura, pericardium and peritoneum, acute inflammatory reactions may appear. Rich primary implantation in the lung may lead to the development of a tuberculous pneumonia. Experimentally, such is the case in rabbits. That these exudative types of inflammation in man are entirely the result of rich implantations is open to doubt. In the serous membranes implantation of the organisms must be secondary to a primary focus. This being true, it is conceivable that the primary focus has so influenced the body that new implantations result in more violent reactions. The tuberculin reaction is almost certainly an allergic manifestation; it persists in the body after the establishment of a primary lesion; the acute inflammatory types of tuberculosis are to be grouped in the same general category, but need not be regarded as purely allergic.

In the serous membranes, the acute reactions show an outpouring of leucocytes, lymphocytes and a fair amount of fibrin formation. In most instances the number of leucocytes is less than that of the lymphocytes and endothelial cells. Tuberculous pneumonia is characterized by considerable edema, moderate fibrin formation and infiltration of leucocytes, lymphocytes and endothelial cells in the alveoli. Necrosis of the exudate and of the tissues involved is common in these diffuse types of tuberculous inflammation. In the meninges, it is not uncommon to find small, generally spherical foci of necrosis of the exudate, which may extend and involve the superficial parts of the brain or cord. In the tuberculous pneumonia, necrosis may be much more extensive and involve not only the exudate but also the pulmonary tissue. In these acute inflammations the number of organisms may be extremely great. According to Jobling and Petersen, the necrosis is probably due to the activity of toxic material liberated by the tubercle bacilli. The caseous character of the necrosis is determined by the same factors that determine caseous necrosis in the center of a tubercle, namely, the inhibition of autolytic ferments by the presence of large quantities of soaps of unsaturated fatty acids. In any instance, the presence of a secondary infection with the infiltration of many polymorphonuclear leucocytes will alter the picture so that liquefaction occurs.

Gross Lesions of Tuberculosis.—It is improbable that the earliest form of tubercle is grossly visible except in such a transparent tissue as the eye. Primary discrete tubercles, however, can be seen as extremely minute bodies measuring less than a millimeter in diameter, projecting into a cut surface or upon a serous surface, firm, rounded, sharply demarcated and of gray color. As the lesions become larger, however, the color is changed by the central

caseous necrosis and the mass becomes yellow. Both these forms of lesions are spoken of as miliary tubercle; the earlier as the gray miliary tubercle and the later as the yellow miliary tubercle. These are called miliary because they approximate the size of a millet seed. Conglomerate tubercles are formed by the fusion of neighboring miliary tubercles or by growth of, and fusion with, secondary or daughter tubercles as described above. The conglomerate

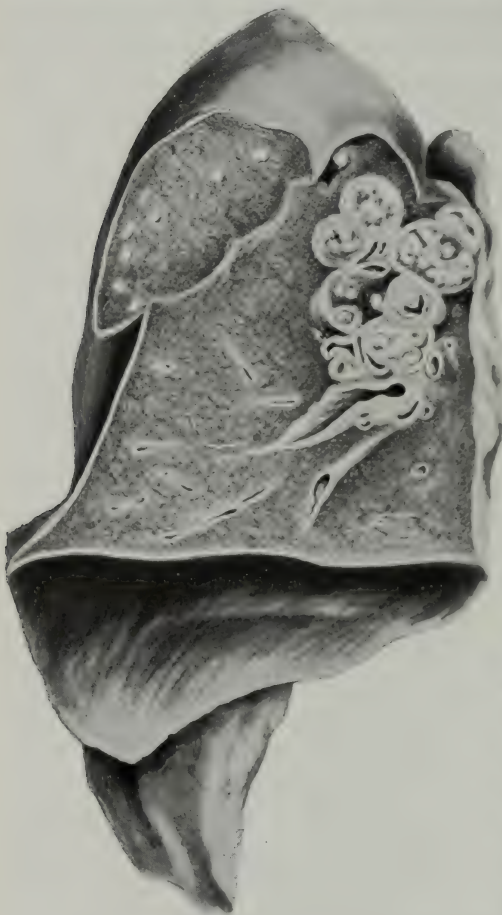


Fig 96—Conglomerate tubercles in hilus of lung and peribronchial lymph nodes.

tubercle is larger than the miliary tubercle and may attain considerable size. It shows the central caseous mass characterized by a relatively dry, finely granular, yellow, often somewhat soapy cross section, surrounded by a thin rim of gray material made up of the reacting cells. The color varies from a very pale grayish-yellow to a deep yellow, and the consistence from a firm, slightly friable mass to a distinctly softer, and sometimes almost semi-fluid mass. Secondary infection determines more distinct softening and pus formation. The outline of the smaller conglomerate tubercle may be distinctly irregular or lobulated when the lesion is due to fusion of several miliary tubercles. When the size is greater, attaining a diameter of 0.5 to 1.0 cm. the term conglomerate tubercle is usually employed, but the lesion is sometimes referred to as diffuse tuberculous tissue. The mass may attain a diameter of several centimeters. This lesion is frequently called the solitary tubercle, or if the size be impressive, it may be referred to as a tuberculoma.

Secondary changes in the tubercle are of considerable importance. As the tuberculous mass enlarges or extends, it may grow into and penetrate a surface communicating with the exterior. Thus, tubercle in the lung may involve a bronchus, or bone lesions may communicate with the skin surface either directly or by way of muscle sheaths; tuberculosis of the epididymis may rupture directly through the scrotum; tubercles of the intestinal lining usually rupture into the lumen. Communication with these surfaces exposes the lesion to additional infection by pyogenic organisms and leucocytes infiltrate. They bring ferments which overbalance the antiferment activity

of the soaps of the unsaturated fatty acids, and softening and liquefaction occur. In the lung a cavity is formed, from the bones a sinus leads, and in the intestine ulcers occur. The suppuration incident to the secondary infection may result in rapid extension of the lesion. On the other hand, this infection may stimulate more sturdy granulation than does the tubercle bacillus, and the resulting fibrosis lead to sharp delimitation of the tuberculous process. As Opie has demonstrated in the pleura of the dog, the presence of large numbers of leucocytes may aid materially in direct combat against the tuberculous process. It is generally stated that the chills, fever and night sweats of advanced pulmonary tuberculosis are due to the secondary pyogenic infection, but the capacity of the tubercle bacillus to excite acute inflammation makes it at least possible that these clinical signs in some instances are due to the tubercle bacillus alone.

When the tubercle grows in the neighborhood of vessels there readily occurs a protective thrombosis as the vessel walls are involved. If secondary

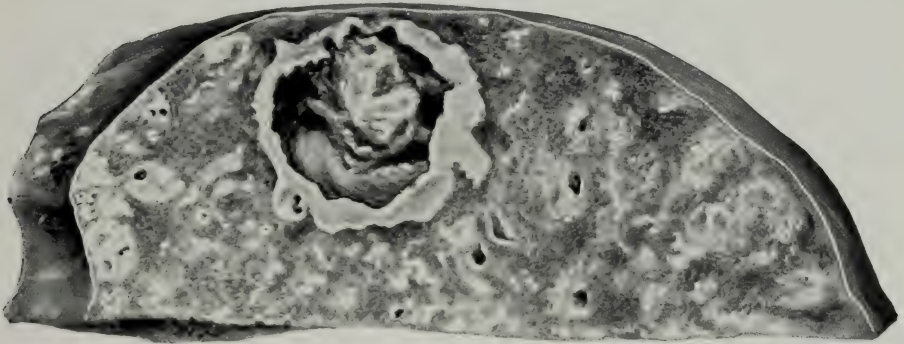


Fig. 97—Small tuberculous cavity in lung.

infection has occurred, this thrombosis is likely to be well pronounced. As the thrombus becomes organized the vessel is converted into a fibrous mass. Involvement externally of bronchi, particularly smaller branches, leads to fibrosis of the walls and finally conversion into a fibrous mass. These are more resistant to the destructive action either of the tuberculous process or of the secondary infection, and in cavities of the lung it is common to find trabeculae made up of these fibrous blood vessels and bronchi.

Tuberculosis may be disseminated in various organs of the body in the condition called disseminated or generalized miliary tuberculosis. The mode of dissemination will be discussed subsequently. Such dissemination usually occurs as the result of a pulmonary tuberculosis but may originate in other secondary situations such as bone or epididymis. The lesions are usually of uniform size, distributed through the substance of the organs. In addition to the lungs, the liver, spleen and kidneys commonly show the miliary tubercles. No organ is immune to invasion in this disease, but the pancreas is only rarely affected, the uterus is usually free and although the pericardium may be tuberculous the myocardium usually escapes.

Later Lesions of Tuberculosis.—Around open lesions of tuberculosis, that is lesions communicating with surfaces, a tuberculous granulation tissue is seen. Resembling non-tuberculous granulation tissue, it is likely to show, however, richer content of lymphoid and endothelial cells and fewer polymorphonuclear leucocytes, and a distinct disposition to undergo caseation necrosis. There are usually giant cells and more or less well defined tubercles. Where resistance to tuberculous infection is manifest there are varying degrees of

cicatrization. This may progress through the intermediation of granulation tissue or may surround non-ulcerated tubercles. Small primary or even secondary lesions may become so densely encapsulated as to arrest the progress of the lesion. Under certain vaguely defined conditions the lesion may permit dissemination of the remaining living organisms, with local extension of the tuberculous process. On the other hand, the surrounding fibrosis may be incomplete or inadequate to arrest the process and the disease becomes chronic. Chronic fibrous tuberculosis shows tubercle formation in places, but is characterized by progressive growth of dense fibrous connective tissue. On surfaces such as the pleura, fibrous adhesions are common. Chronic tuberculosis of the serous membranes often shows extensive hyalinization of the inflammatory fibrous tissue. Calcification is common in the older lesions of tuberculosis. Small lesions may be almost completely calcified after encapsulation and caseous necrosis, yet the bacilli remain alive for many years. It is probable that the soapy materials in the caseous necrosis favor, in a physico-chemical manner, the infiltration and deposition of calcium salts (see Maver and Wells). Calcification also appears in the old

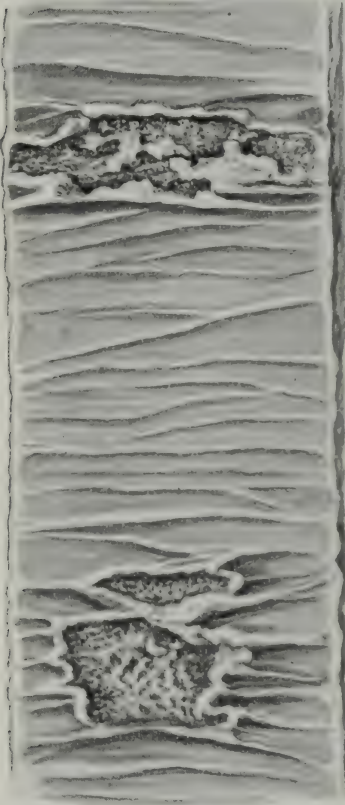


Fig. 98—Tuberculous ulcers of intestine. The upper ulcer has spread laterally along the lymphatics.

fibrosis of chronic fibrous tuberculosis.

Immunity in Tuberculosis.—The tubercle bacillus produces its effects partly as the result of the presence of the bacterial bodies and partly as the result of more or less soluble products of its growth. Prudden and Hodenpyl showed that the inoculation of dead bacilli is followed by the production of tubercles with, however, little tendency to caseation. Ray and Shipman found that defatted tubercle bacilli and the lipins of tubercle, grass and colon bacilli may each induce tubercle formation. These observations do not prove that the bacteria alone are concerned, for soluble products may also play a part. Auclair and Paris have made extensive studies of bacillary extracts in

water and in salt solution, in alcohol, ether, chloroform, in acetic acid, and in alkalinized solutions of neutral salts. They found little pathogenic activity on the part of the saline or watery extracts. Alcohol or ether extracts produced local reaction and caseation; chloroform extracts tended to induce fibrosis. Extracts in acetic acid or neutral salts produced local lesions as well as general hyperemia, disturbance of the hematopoietic system, cachexia, and death. There is no doubt that these extracted substances have much to do with the invasion of tubercle bacilli. Armand-Delille described general symptoms resulting from inhalation of volatile products of cultures. That these are toxins in the immunological sense is open to doubt, and Krause states that "it is the general opinion that no true toxin of the microorganism has ever been demonstrated." It is then rather in the nature of hypothesis to regard such extracts as those of Auclair as endotoxins and the tuberculin of Koch as

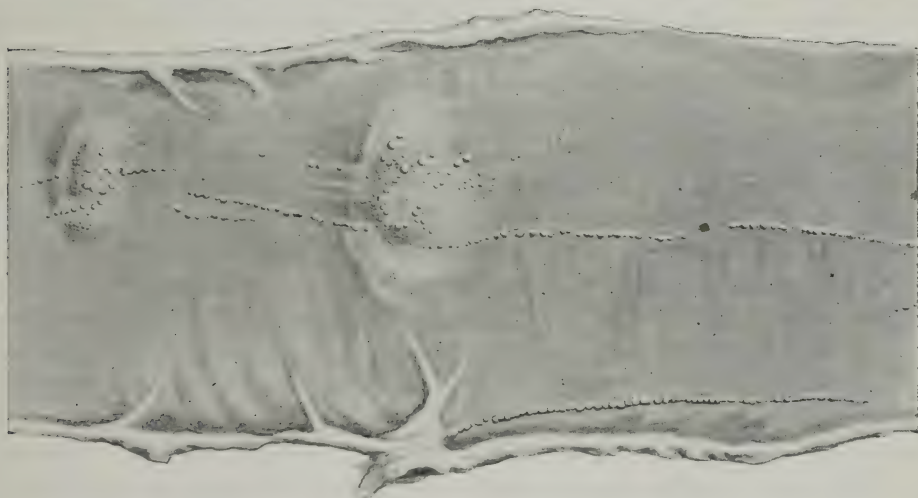


FIG. 99.—Miliary tubercles of peritoneum of intestine opposite ulcers. Intestinal lymphatic vessels show lines of miliary tubercles.

exotoxin. Tuberculin, however, is a body which in the presence of tuberculosis leads to specific reactions and certainly is in some way closely related to the substance or substances associated with local and general manifestations of the disease. Controversy over these disputed points leaves still open the question as to exactly how the tubercle bacillus operates. Certain features of immunity have been fairly well worked out and these will be enumerated.

That the tubercle bacillus produces a toxin or toxins is still in doubt, since the injection of various toxic products leads to the production of no clearly demonstrable antitoxin. Agglutinins and precipitins have been demonstrated in animals by Petroff; they disappear as the disease becomes advanced. In man they are rarely found. Complement fixation is demonstrated experimentally and in human disease; the reaction is most marked in active stages of the disease and tends to disappear in the quiescent stages.

The various types of tuberculin reaction are of great importance clinically, and the results have been widely utilized in epidemiology and in hypotheses

concerning the immunology of the disease. The tuberculin may be applied intradermally, subcutaneously (for general reactions) or in the conjunctival sac. Positive local reactions are of inflammatory character; positive general reactions are febrile. The exact nature of the reaction is open to question. Koch believed the reaction due to a superaddition of toxic material to that already present. Others have regarded it as a toxin-antitoxin reaction. Calmette considers it a reaction of precipitation, in general accord with the widespread view that it is a manifestation of hypersusceptibility. Krause is of the opinion that this reaction occurs under the same conditions as does immunity to infection, and that the one may be a function of the other. There can be no doubt that the reaction appears very soon after infection; it persists during the presence of the disease, but decreases and may disappear during active progress of the disease. Its specificity is extremely high, and it has been found present in cases where the actual demonstration of the disease has been possible only upon animal inoculation. It cannot be regarded as indicative of immunity to tuberculosis particularly in view of experiments on reinoculation to be mentioned subsequently. That the subcutaneous injection of tuberculin may excite a latent lesion to renewed activity is unquestioned; that it does so with any degree of frequency is doubtful. This phenomenon may be explained upon the theory of augmentation of toxic products at the site of the lesion, or upon the theory that a local reaction of hypersusceptibility operates to produce renewed activity.

Tuberculosis is a disease of civilization. Cummins points out that members of isolated communities, where tuberculosis is rare or absent, show a marked susceptibility to the disease, whereas in infected communities the individuals are distinctly more resistant. He claims that the susceptibility of African and other primitive races is the susceptibility of "virgin soil." Nevertheless, the susceptibility of these races when transplanted to civilization may be in part due to inferior hygienic conditions. The resistance of civilized man to clinical disease may be due to inheritance of resistance, because of the failure of survival of the susceptible. On the other hand, it has been pointed out that practically all civilized populations are infected in early life. The clinically manifest disease, however, is milder in such peoples than in primitive races. Unless resistance were originally present the primary infection should be more severe and exhibit more serious immediate results. The primary lesions, as is well known, are usually inactive throughout life. If the individuals acquire an immunity as the result of a lesion which has been resistant and cicatrized, they should not be susceptible to reinfection. The studies of Brown and Gardner on clinical and experimental material, indicate that reinfection can occur but do not convincingly prove that the reinfection is by the same strain as that originally involved. That this reestablishment of active disease is due to a diminution of any known immune substances is probable but not proven; that it is the result of impoverishment of general resistance by insufficient food and rest, or as the result of other disease such as measles and influenza, is highly probable. Reactions to tuberculin tend to disappear during the course

of acute infectious diseases. If the reaction be a manifestation of immunity, the resistance is reduced during the acute infectious disease.

The tubercle is surrounded by a wall of lymphocytes. Jobling and Petersen have demonstrated a lipase in lymphocytes and suggest that this may attack the bacilli by dissolving the waxy shell, but Reed was unable to find such a ferment. Pavlow, however, found that lymphocyte extracts destroy tubercle bacilli. Murphy and his collaborators have found that destruction of lymphocytes in the body by use of the x-ray, reduces resistance to tuberculosis. Endothelial cells, particularly those of the liver and spleen, have a high phagocytic power for tubercle bacilli, as is true also of the giant cells. Anatomical studies indicate that cellular reactions constitute a most important defense against tuberculosis and play a large part in its arrest.

Dissemination of Tuberculosis.—The dissemination of tuberculosis may occur through the blood stream, the lymphatic stream, over surfaces, by direct extension or, as Permar points out, by the migration of endothelial cells which contain bacilli. The growth of tubercles may involve blood vessel walls, either veins or arteries. If protective thrombosis does not occur, the tubercles may project into the lumen of the vessel and tubercle bacilli thus gain access to the blood stream. In more rapidly extending lesions, preëxisting tubercles may rupture directly into the blood stream. In the case of rupture into a pulmonary artery, the dissemination through the blood stream may be limited to the part of the lung supplied by that artery. In most cases, however, rupture into the blood stream determines widely disseminated tuberculosis throughout the body. This so-called generalized miliary tuberculosis usually shows lesions in various organs of about the same size and presumably of about the same age. It is therefore assumed that generalization results from rupture of a lesion through the vessel wall, thus discharging into the blood stream at one time a large number of organisms, a "shower" of tubercle bacilli. Nevertheless, smaller discharges of tubercle bacilli into the blood stream must occur. On this basis are explained tuberculous lesions of bones and joints as well as those of the genito-urinary tract, of the meninges and of other situations, in which transmission from the primary focus of infection must be by the blood. According to Krause, the secondary tubercles arise not within the blood vessels but in the immediately neighboring tissues; the bacteria must penetrate the tissues before they produce lesions. Dissemination through lymphatic tracts is much more common, but does not result in such widespread lesions as dissemination through the blood channels, except where a tuberculous thoracic duct supplies organisms to the blood stream. Tubercle bacilli may be carried in the lymphatic stream either free or within phagocytic cells. Lesions are most commonly established in lymph nodes which drain the affected areas. Nevertheless, tubercles may also appear in the walls of lymphatic vessels. This is particularly well seen in the lymphatics of the intestine about an area of ulceration of the mucosa. In certain situations, particularly the lung, the involvement of draining lymph nodes may block them so that no further drainage is possible. The consequence is a retrograde

flow of lymph from the tracts entering the nodes backward through other channels to other nodes. Involvement of the nodes of the hilus of the lung may cause retrograde flow of lymph through the lung toward the pleura, and consequent dissemination of tuberculosis along the perivascular and peribronchial lymphatics. This results in the formation of numerous tubercles about the vessels and smaller bronchi, the so-called peribronchial and perivascular tuberculosis. Dissemination over surfaces is observed sometimes in the lung, where aspiration of tuberculous material along the bronchial tree may result in secondary tuberculous foci in the branches. There is little doubt that a few foci in the peritoneum may spread over that surface by direct dissemination and the same is undoubtedly true in relation to pleura, meninges, and pericardium. Patients with a long standing tuberculous cavity of the lung

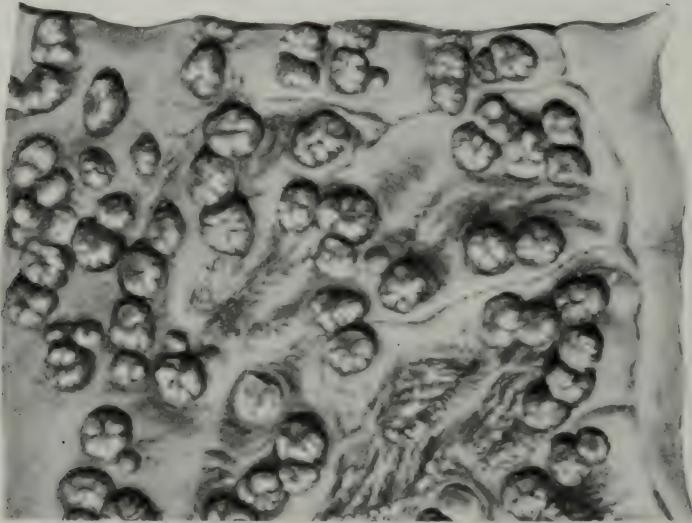


FIG. 100.—Perlsucht disease, large fibrous conglomerate tubercles in mesentery of cow.

frequently have an associated ulcerative tuberculosis of the intestine. This may be due to swallowing of organisms in the sputum. It might be expected that the gastric secretion would destroy the bacilli, but such work as that of Hoefert and of Kopeloff leaves no doubt that with reduced acidity, bacteria survive exposure to gastric juice. Calmette is of the opinion that intestinal involvement is more frequently due to dissemination through the blood stream than by swallowing. It might also be due to transfer by migrating phagocytic endothelial cells. Dissemination by direct extension is seen in those instances where enlargement of a focus in a lung involves the pleura. Similarly, tuberculosis of the spinal vertebræ may extend directly and involve kidneys or other neighboring organs. Tuberculosis of the ends of bones may extend directly into joint cavities. Meningeal infections are sometimes observed as the result of direct extension from tuberculosis of the vertebræ and more rarely of the cranium.

Heredity and Tuberculosis.—When it is considered that the phenomenon of heredity is the transmission of characters through the germ plasm, it is obvious that infectious disease cannot be, strictly speaking, heritable. There remain for consideration, however, the problem of inheritance of constitutional predisposition and that of congenital infection. It is noted that thin skinned, blond, gazelle eyed individuals with long, narrow, flat chests are commonly victims of tuberculosis, and there is no doubt that such physical characters are heritable. Hayek points out the great difficulty of correlating constitution and disease, and indicates clearly that any relationship between constitution or

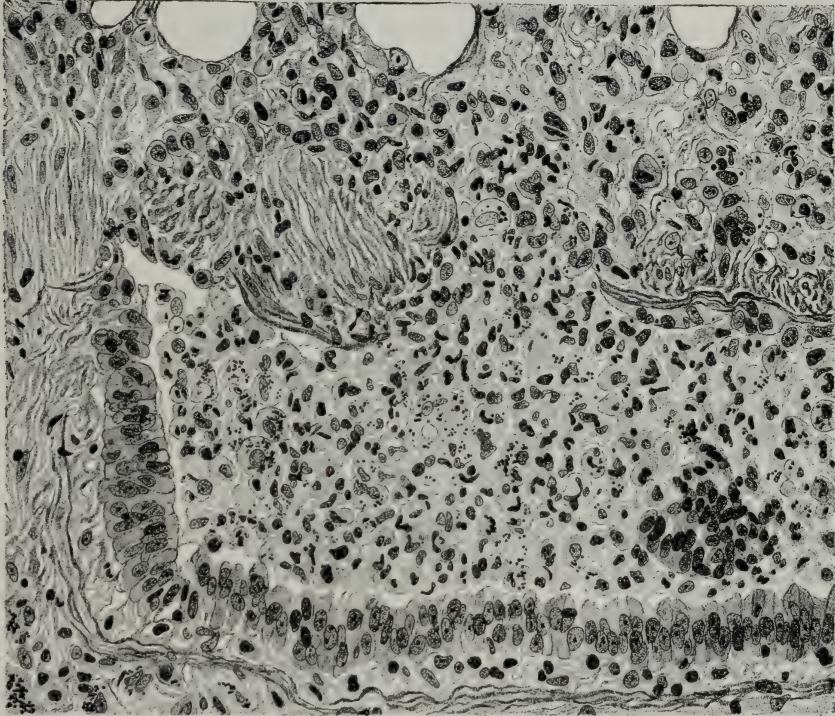


FIG. 101—Early tuberculous pneumonia. The exudate is largely within the bronchiole, but similar exudate occurs in alveoli. There is desquamation of alveolar epithelium and an exudate of leucocytes, lymphocytes and phagocytic endothelial cells. Nuclear and cellular fragments within the phagocytes are indicative of considerable necrosis.

disposition, as indicated by physical characters, and tuberculosis has yet to be proven. That tubercle bacilli can enter the fertilized ovum either by way of ovum or spermatozoon seems unlikely; such an infected ovum would probably not develop or the infection would lead to the early death of the embryo.

Tuberculosis in early life is usually in the form of a minor primary lesion. Occasionally generalized miliary tuberculosis occurs in the very early months of life; we have observed one such case in an infant two months old. Whether such cases are of congenital prenatal origin or are postnatal infections varies with individual cases. Certainly most cases of tuberculosis represent postnatal infections, but if the tuberculin test can be relied upon as an index, most postnatal infections do not occur until after the infant is from four to six months

old. Whitman and Greene have collected one hundred and thirteen cases of prenatal infection either of placenta or fetus or both, and add seven additional cases including one of their own. This does not exhaust the possibilities in this direction for numerous cases must have escaped detection. Nevertheless, the number is relatively small in proportion to the enormous number of children, free from disease as determined by clinical examination and the tuberculin test, born of tuberculous parents. Congenital tuberculosis must come, in the vast majority of infants, from the infected mother. There are a few cases on record in which tuberculous infants were stillborn from mothers whose clinical examination showed no tuberculosis, whereas the fathers were obviously tuberculous. While it must be admitted that tuberculosis may be of congenital origin, there is little doubt that most infections are postnatal. If infants be removed from tuberculous parents early in life they may escape the disease, but if contact be maintained they usually become victims. It is possible that some of the infections are due to milk from the mother, but the likelihood of this is not great since the obviously tuberculous mother is unwilling to expose her infant in this way, or is unable to nurse. The majority of these infections come either directly or indirectly from the sputum of the tuberculous parent. Infection by bovine bacilli comes principally from cow's milk.

LEPROSY

Introduction.—Leprosy is a chronic infectious disease affecting the skin and nervous system, due to the bacillus *lepræ* of Hansen, discovered in 1871. The disease seems to have originated in some part of the Orient, probably India, and transmitted in epidemics and by infected individuals, has appeared in practically every part of the world. Nevertheless, it appears to be more frequent and more firmly established in endemic form in the tropics than in temperate countries.

The Bacillus *Lepræ*.—In a review of the literature by Wolbach and Honeij, it is stated that since Hansen's discovery no less than twenty-six authors have reported on organisms grown from the lesions of leprosy. The organisms so isolated may be considered to fall into four different groups. The group which usually is described as the Babes-Kedrowski organism, is of the diphtheroid type and is partially acid-fast or acid-resistant. It may grow so as to form branching filamentous organisms of the general type of streptothrix. Repeated injections of this organism into animals may reproduce local lesions somewhat resembling those of leprosy. Another group is that which has been extensively studied by Clegg and his collaborators, namely, an acid-fast organism which is chromogenic and produces yellow colonies. The third group includes acid-fast organisms which are anaërobic in growth, first reported by Ducrey. The fourth group includes acid-fast organisms of aërobic character which are not chromogenic. This group was first described by Karlinski and has been extensively studied by Duval. Duval was unable to isolate from leprosy, organisms of the streptothrix type and maintains that his slow growing organism is the probable cause of leprosy. Duval's studies indicate that several varieties of acid-fast organisms including the hay, milk, butter and smegma bacilli may produce lesions practically identical with those of leprosy and he is therefore inclined to believe that organisms isolated from leprosy, which produce similar lesions cannot positively be identified as the cause of the disease. Because of the isolation of organisms, which in colonies show streptothrix-like growth, it has been assumed that the leprosy bacillus is not truly a bacillus but is probably to be grouped with streptothrices. Duval is definitely of the opinion that this is not true and that the causative organism is an acid-fast non-chromogenic bacillus. In contrast to the views expressed by numerous bacteriologists who have cultivated supposedly leprosy organisms, Castellani and Chalmers state that the generally accepted view of most workers in the field is that the bacillus of leprosy has never been grown in pure culture.

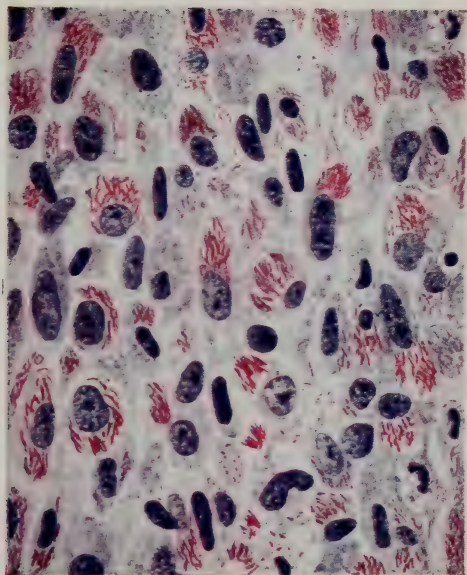
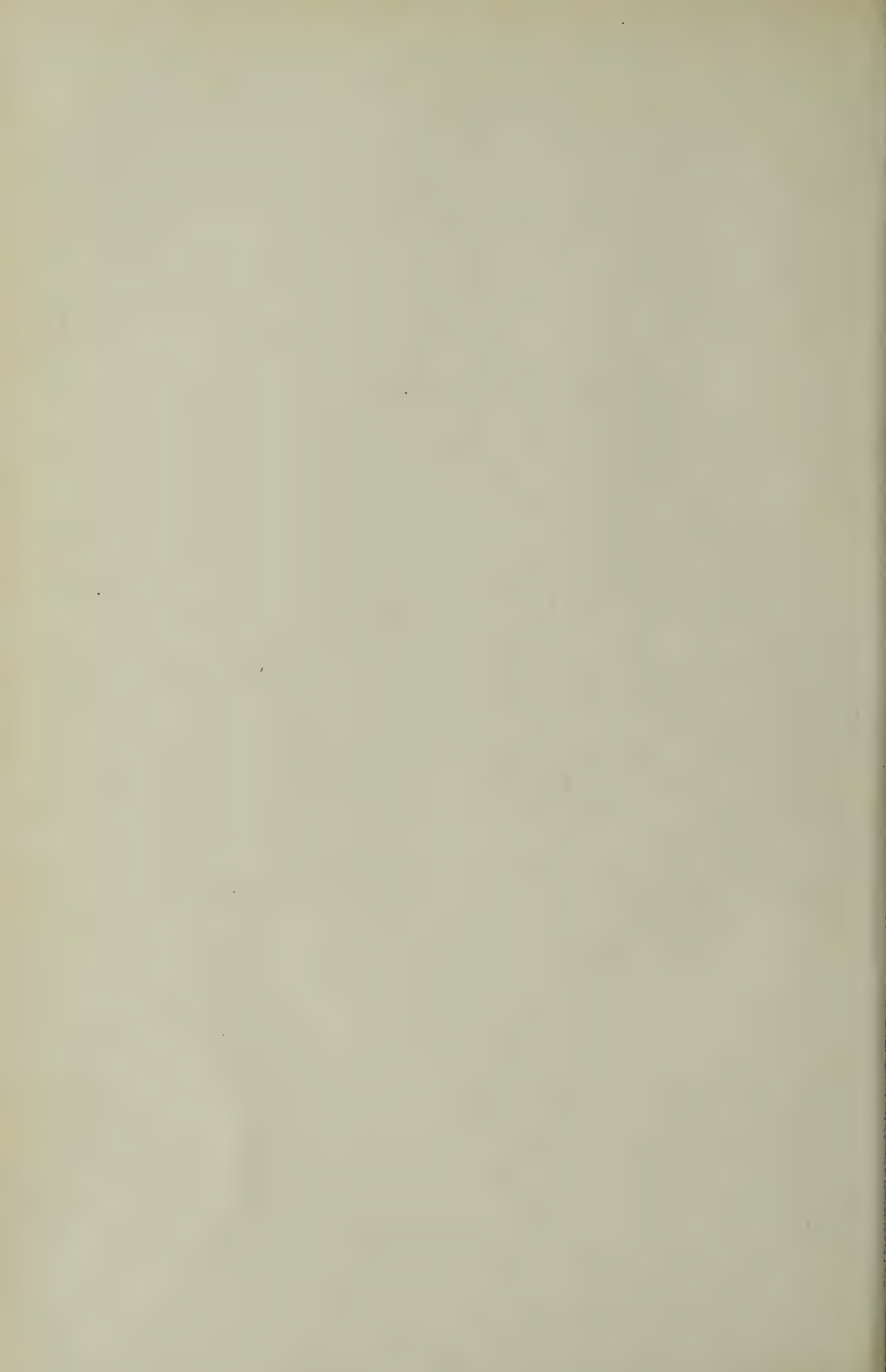


PLATE IX—Lepra bacilli in cells of nodule.



Clinical Manifestations.—Transfer of leprosy from one to another is probably only by direct contact. The period of incubation is unknown but probably extends over several months. The disease may occur as tubercular leprosy, *lepra tuberosa*, or as maculo-anesthetic leprosy, *lepra anæsthetica*. Not infrequently the first lesion is in the nasal mucosa. In both forms the development of lesions may be accompanied by fever, malaise and other general symptoms. In the tubercular form the lesions occur principally in the skin, as firm, usually painless, projecting small nodules, at first light blue or pink in color and later pale yellow or without color. They may be found in

FIG. 102

FIG. 103

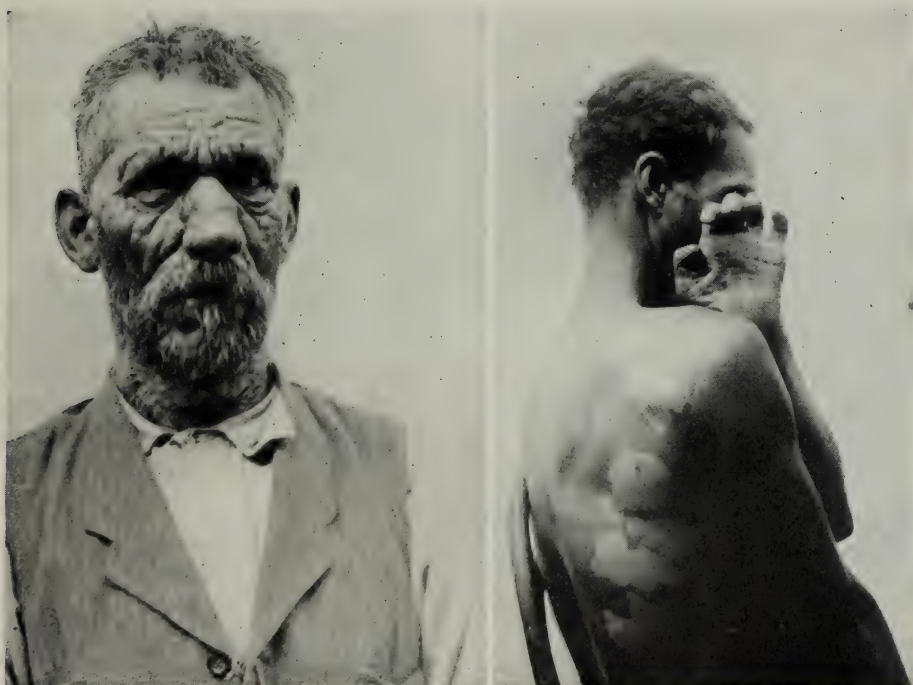


Fig. 102—Photograph of nodular leprosy, showing leonine character of facies and loss of hair of eyebrows.
Courtesy Guthrie McConnell, M. D.

Fig. 103—Photograph of maculo-anesthetic leprosy, showing depigmented macules on back and claw-hand.
Courtesy Guthrie McConnell, M. D.

mucous membranes but are observed more or less widely disseminated over the skin and as they occur on the forehead and face may cause the so-called leonine face. They sometimes ulcerate.

In the maculo-anesthetic form of the disease there are found pigmented, non-pigmented or depigmented cutaneous papules or macules. The patches are often dry and scaly and the skin is thin and atrophic. Both over these patches and over the tubercular nodules, the hair drops out. The anesthesia is first of temperature, then of pain and finally of tactile sensation. Trophic changes may occur in the muscles and result in partial paralysis. The anesthesia permits ready traumatic injury and pyogenic infection. Therefore, the extremities, especially fingers and toes, may become diseased partly as the

result of trophic change and partly as the result of traumatic infection. This leads to deep infection, gangrene, and sloughing off of parts of extremities, resulting in varying degrees of deformity. It is not uncommon to find an association of both the tubercular and the maculo-anesthetic form of leprosy. The disease runs a course prolonged over months and years, and ultimately is fatal. Recently, however, favorable therapeutic results have been achieved in early cases by the use of chaulmoogra oil and its derivatives.

Pathological Anatomy.—The leprous nodules vary in size from a few millimeters to one or two centimeters. They are sharply defined and show a somewhat tense, overlying epiderm. They are firm and cut with considerable resistance. Upon being opened, the cut surface bulges slightly and shows either a light gray or a pale yellow surface. The lesions are in the corium, but may

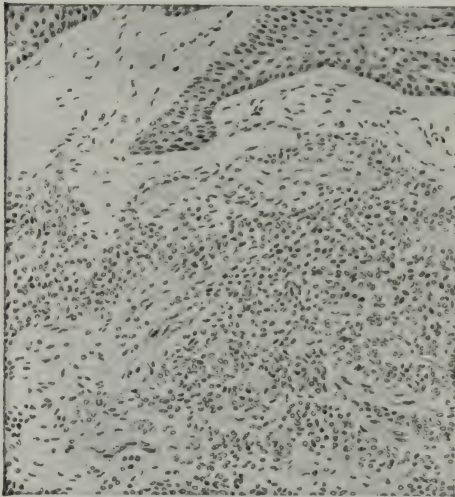


FIG. 104—Histological appearance of lepra nodule.

occasionally be found in the subcutaneous tissue. The macules show grossly thin, atrophic epiderm and corium, either pigmented, of normal color, or with reduction of pigment. Histologically, the leprous nodule is found to be made up of a large collection of mononuclear cells. Many of these cells appear vacuolated with ordinary stains but are found by special staining, to contain acid-fast bacilli. It is stated that the lesions begin as a perivascular infiltration of plasma cells which gradually becomes more and more extensive until the entire nodule is made up of these mononuclear cells. In the fully developed lesions, the cells have lost the

character of plasma cells and appear more nearly like endothelial cells. A moderate degree of fibrosis is associated, becoming more marked as the lesions become older. Special stains, according to MacCallum, show considerable content of fat within the nodule. Stained by carbolfuchsin and lightly decolorized, there are found large numbers of acid-fast bacilli. These are fairly long, slender rods, sometimes beaded. They appear either within the large mononuclear cells clumped together, or in small masses referred to as globi. The globi are regarded by some as clumps of bacteria which have accumulated about them a small mass of exuded material, and by others as intracellular organisms which have caused the death of the cell and appear simply as clumps with a small areola about them. Free extracellular organisms are also likely to be found.

The nerve trunks, upon gross examination, are found to be somewhat enlarged and in the living patients may present firm, more or less tender cords. Enlargement is not uniform but appears in nodular character throughout the

length of the nerve. Microscopic examination of the nerve shows that the epineurium and the endoneurium are infiltrated with cells similar to those found in the cutaneous nodules. These large round cells are distributed irregularly through the connective tissue and are sometimes associated with fibroblasts. Bacterial stains show the presence of organisms within cells, in globi and free in the intracellular and interneural spaces. Special stains show degeneration of the myelin sheath and of the axis cylinder. The same condition may be found in nerve trunks in tubercular leprosy. Although the lesions of leprosy are confined particularly to the skin, the mucous membranes and the nervous system, nevertheless, bacteriological examination shows the presence of the acid-fast bacilli in practically every organ of the body. It therefore seems probable that leprosy represents, at least at some time in its course, a bacteremia.

After leprosy has continued for a long time, the patients are likely to show general fibrosis of many of the internal viscera. In certain cases amyloidosis may occur. Tuberculosis and syphilis may be associated with leprosy.

Immunity.—Uncertainty as to isolation of the organism of leprosy makes it impossible to give positive statements in regard to immune bodies. Nevertheless, agglutination of the organisms isolated has been described. It is also possible to immunize animals, particularly with the organisms of Duval, so as to produce complement fixing bodies. The periodic occurrence of crops of leprosy lesions, showing a cyclic development somewhat like that of syphilis, makes it seem probable that during the course of leprosy allergic phenomena occur similar to those to be described in syphilis.

GLANDERS

Introduction.—Glanders is a specific infectious disease, which, more particularly in the prolonged and chronic cases, exhibits lesions which microscopically are definitely granulomatous. Although principally a disease of the horse and ass, it affects other animals and occasionally is observed in man, particularly those in contact with horses. It has also been observed in man as a laboratory infection. The disease has been known since the middle ages and is one of the first in which definite infectious character was demonstrated, this having been proven in the latter part of the eighteenth century.

The organism, *bacillus mallei* of Loeffler and Schütz was discovered in 1882. It is a non-motile bacillus measuring 0.5 x 3 or 4 micra. Proper staining shows it to be somewhat beaded in form and it is gram negative. It grows with some difficulty in primary culture but after establishment on media grows readily. The organism is aerobic and its growth is favored by the presence of glycerin or of dextrose. Of the laboratory animals, the rabbit can be infected but the guinea pig is much more susceptible. It is not particularly resistant to the destructive influences of environment outside the body. Upon injection into the guinea pig subcutaneously, there occurs within a few days a somewhat putty-like induration at the site of injection followed by radiating bands of infiltration in the neighborhood. The neighboring lymph nodes are also enlarged. Of particular interest is the Strauss test which, in the hands of Frothingham and others, has been found to be an important method of making the diagnosis of glanders. The suspected material is placed in suspension in sterile water or in salt solution, and inoculated intraperitoneally into the guinea pig. Within two or three days there is swelling of the spermatic cord, followed rapidly by enlargement of the testicles. This is followed by breaking down and if the animal be allowed

to live leads to a superficial discharge of pus from the lesion. In this part organisms are easily obtainable. At autopsy the peritoneum is likely to be involved in a more or less marked peritonitis. The culture is made upon potato and produces amber or yellow colonies.

Clinical Features.—Both in horse and in man the disease may appear in either acute or chronic form. In man the acute form shows an incubation period of four to eight days and is usually fatal within three to four weeks. Infection is usually by implantation in the nose, or in abrasions or cuts in the skin, of material from infected horses. There develops at the site of inoculation a red, swollen papule which rapidly becomes pustular and then breaks down leaving an ulcer with granular base and undermined edges. The disease is febrile and may be introduced with chills or other violent symptoms. Enlargement of the regional lymph nodes is common, and cases are likely to show a more or less diffuse erythematous or erythematopapular eruption. Beginning in the nose, the first symptoms may be the discharge of bloody mucus, following which the local and general symptoms progress as described. Extension from the nose may involve the pharynx, the soft palate and larynx. The spleen and liver are likely to be enlarged and not uncommonly rheumatic pains in the joints are observed. Secondary subcutaneous nodules may occur which soften and ulcerate. In the chronic form, the incubation time is probably longer and the development of the individual lesion is slower. The local and general symptoms are not so severe. The superficial lesions are sometimes taken for syphilis, and metastasis in the deeper tissues of the body may resemble tuberculosis. Although practically all acute cases die, according to Kolle and Hetsch about half the chronic cases recover spontaneously.

The acute disease in the horse is very much like that in man, prostration is extremely marked and the outcome is usually fatal. The chronic disease in horses may last over years, with discharge from the nose, and after the course of time, considerable destruction of the nasal septum. In addition, the lymph nodes are enlarged and not uncommonly break down. These are the farcy nodules, particularly likely to be seen along the tendons of the extremities, either as deep-seated putty-like nodules or as somewhat deep eroding ulcers.

Pathological Anatomy.—The superficial lesions are described above, but on cutting into these we find that as a rule, there is some reactive fibrosis in the surrounding tissue. Of the internal viscera, the lung is most likely to show specific lesions. In the lung the lesion appears somewhat like small conglomerate and large conglomerate tubercles, although in some instances there is a resemblance to bronchopneumonia. The spleen is the seat of an acute hyperplastic enlargement. The liver, kidneys and heart are likely to show cloudy swelling or fatty degeneration. Microscopically, the lesion differs with the duration of the disease. The study of the disease in man and animals, as well as by experimental methods, indicates that the lesions probably vary depending upon the virulence of the organism. Baumgarten described the lesion as a chronic granuloma, somewhat similar to tuberculosis. Wright and others describe it as a destructive lesion of the tissues followed by acute inflammatory exudation. Duval and White point out that in experimental animals lesions of different types are produced, depending upon virulence.

The more virulent organisms produce an early destruction of tissues, followed rapidly by an infiltration of leucocytes and formation of fibrin. Less virulent organisms produce little or no immediate destruction of the tissues, but their injection is followed rapidly by an inflammatory infiltration. Organisms of low virulence produce primary tissue proliferation with epithelioid cells in large numbers, and giant cell formation. As ordinarily seen in man the lesions show various foci, with central necrosis of the tissues and of the exudate. Karyorrhexis of tissue nuclei and of the nuclei of invading leucocytes, as well as pyknosis, lead to the formation of irregular and bizarre masses of chromatin. In the neighborhood are found masses of polymorphonuclear leucocytes with a few lymphocytes. Fibrin may be present in the form of small fibrils. In addition, irregular masses of epithelioid cells are observed, either outside a layer of leucocytes or immediately adjacent to a necrotic area. Giant cells are not common in the human lesion, but may be found in the form of typical Langhans' giant cells or more nearly like the foreign body type of giant cell. Granulation tissue is often abundant. Hemorrhage is not uncommon. The bacilli may be demonstrated in the large endothelial cells or in the giant cells. Duval calls attention to lesions of the smaller blood vessels, in which there is fatty degeneration of the musculature underlying the intima, preceded by, or associated with, proliferation of the intimal endothelium. Lesions examined microscopically early in the disease show principally necrosis and suppuration, whereas those examined later show a greater prominence of epithelioid cells. Provided the lesion be old enough, there appears in the marginal areas a considerable amount of reactive fibrosis. Pulmonary lesions show in the neighborhood of the glanders nodule a reactive bronchopneumonia which may exhibit organization.

Immunity.—Infection with glanders leads to the elaboration of precipitins, agglutinins, and complement fixing bodies, and in addition, the development of hypersusceptibility to the soluble products of the organisms. The latter may be demonstrated either as a general reaction to subcutaneous inoculation or as an ophthalmic reaction. The presence of these immune bodies has led to various immunological tests for the presence of the disease. Agglutinins are at their height at the fifth and eleventh day of the disease. Complement fixing bodies appear at about the same period or slightly later. The general reaction to the soluble product, mallein, appears at about the fifteenth day. The ophthalmic test is only reliable after infection has lasted for about twenty-

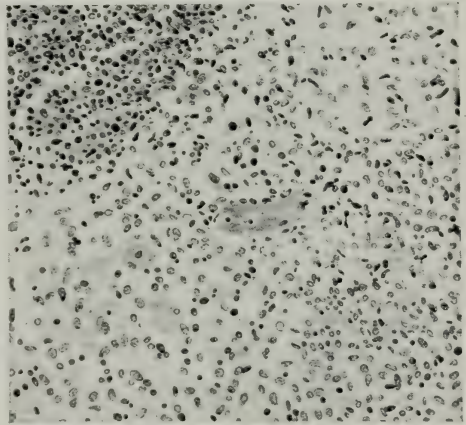


Fig. 105—Histology of glanders. Note the variety of cells present and in the upper part of the field the pleomorphic character of chromatin masses.

one days. Mallein may be prepared by making a watery or glycerolized extract of the cultures or may be prepared in very much the same manner as is tuberculin. Subcutaneous injection leads within a few hours to a fairly large local reaction with tenderness, swelling and redness. The body temperature rapidly becomes elevated and may not return to normal for several days, but sometimes the appearance of fever is delayed. Instillation into the conjunctival sac is followed rapidly by inflammation and even suppuration of the conjunctiva. The mallein test is commonly employed in veterinary practice and is considered to be highly specific. In the hands of Povitsky it was found desirable to test animals by the ophthalmic reaction, complement fixation and agglutination test; positive reactions with any one of these tests more than overbalance negative reactions with the other tests, and all three should be negative in order to pronounce the animal free from the disease. Mason and Emmons state that the concensus of opinion is that agglutination gives a greater percentage of positive results in acute cases and complement fixation is more reliable in subacute or chronic cases.

Finger showed that animals can be immunized against glanders by repeated subcutaneous injection or intravenous injection of killed cultures, but this is not an absolute immunity. Similarly rabbits which survive a generalized glanders infection are subsequently resistant to the inoculation of virulent organisms. Treatment with mallein or with vaccine has not been followed by great success, although recently good results have been reported in cases of chronic glanders. The chronic disease, however, tends toward spontaneous recovery in about half the cases and the results with vaccine cannot as yet be accepted as definitely beneficial.

RHINOSCLEROMA

Introduction.—Rhinoscleroma is a chronic, granulomatous process which affects the nose, the adjacent mucous membranes and sometimes the adjacent skin. The disease is endemic in many parts of the world but is most frequent in southeastern Europe, "the shores of the Danube." In the United States, it has been seen usually in foreigners. Although described by Hebra and Kaposi in 1870, its pathological identity was established in 1882 by Frisch. The bacillus rhinoscleromatis of Frisch is constantly present in the lesion and can be grown in pure culture, but the disease has not as yet been produced experimentally in animals. This organism is very closely related to the bacillus pneumoniae of Friedländer. The colonies of bacillus rhinoscleromatis are somewhat more gray and the organism tends to retain its capsule in culture. It is distinctly less pathogenic for animals than is the pneumobacillus, and according to Frisch does not coagulate milk nor produce gas in sugars. According to Bailey it does not acidify maltose. Perkins' studies lead him to believe that bacillus rhinoscleromatis is a degeneration product of Friedländer's bacillus and that it is not the cause of the disease but merely a secondary invader. Pardo-Castello and Dominguez isolated bacillus lactis aërogenes in pure culture from a case, which on clinical and histological grounds was rhinoscle-

roma. Most investigators are convinced that bacillus rhinoscleromatis is the cause of the disease, and Bailey maintains that the organism is sufficiently characteristic to justify regarding it as a distinct species. Infection is probably by direct contact, since the organism is an obligate parasite and is contained in the nasal secretions of the patients.

Pathological Anatomy.—In the large majority of cases the disease begins in the nasal fossæ and, although progressive, is confined to the upper respiratory tract. The early lesions are small, firm, dark red nodules which enlarge, coalesce and extend by the production of new nodules. The nodules may attain a

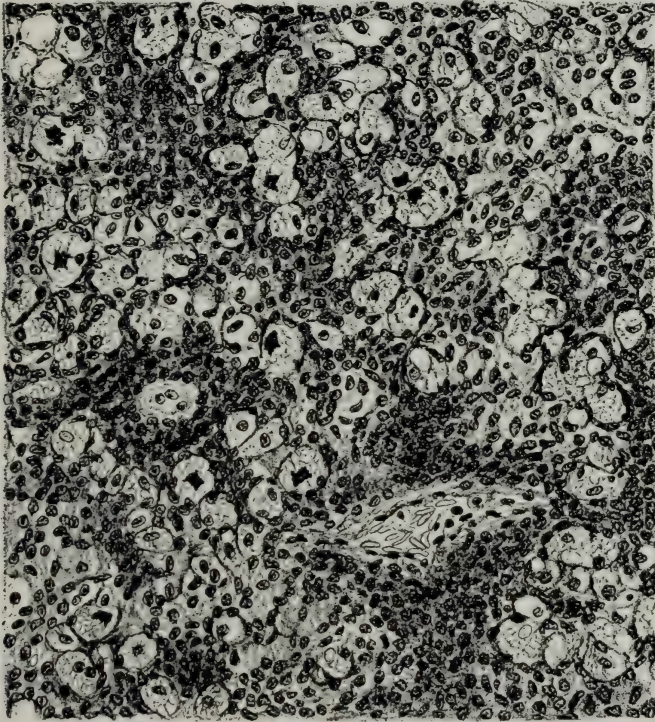


Fig. 106—Histological picture of rhinoscleroma. Note the vacuolated Mikulicz cells with eccentric crumpled nuclei.

diameter of 1.5 or 2.0 cm. The earlier extension is into the pharynx and soft palate; extension to the larynx may cause asphyxia. The process may extend anteriorly and involve the anterior nares and the upper lip. Although the lesions may bleed freely on manipulation, ulceration is not common except in the pharynx and soft palate. The nodules occupy the mucosa and underlying tissue; they cut with resistance and show a pale red, bleeding, reddish-gray, slightly retracted cut surface.

The microscopic picture is characteristic. There is a mass of plasma and lymphoid cells, the latter predominating toward the surface. The lesion is fairly well vascularized, and although the connective tissue within it may be somewhat atrophic, it is abundant in the outer parts and around the cell mass.

Certain large cells may contain the hyaline, acidophilic, Russell fuchsin bodies and the latter may appear in the tissues. The striking cells are the Mikulicz cells, which are either irregularly distributed through the lesion or are clumped in masses of a dozen or more. These are large oval or round cells, four to five times the diameter of the plasma cell. The cytoplasm contains large vacuoles known to be neither fat nor glycogen. They contain the bacilli either sparsely around the margin of the cell or crowding the entire cytoplasmic mass. Fine technique may demonstrate capsules. The nuclei are relatively small, frequently pycnotic and so shrunken as to present a serrated outline. Most of the earlier students were of the opinion that these cells are enlarged and degenerate plasma cells, but Alagna believes that they also originate from macrophages of connective tissue. The vacuoles probably are the result of the presence in the cells of the bacteria, although other hypotheses have been offered.

Immune Reactions.—Bailey found that the serum of a patient fixed complement in the presence of both homologous and heterologous strains, in higher dilutions than Friedländer's bacillus or bacillus *aërogenes capsulatus*. Precipitin and agglutination reactions were not specific. Anderson found that vaccines were not permanently beneficial to one case so treated.

The disease usually terminates fatally although in recent reports radiation has been distinctly beneficial. Stelwagon reports a case in which malignant change occurred.

SYPHILIS

Introduction—Syphilis, or lues, or great pox, is a specific infectious disease due to an organism variously named *spirocheta pallida*, *treponema pallidum*, *spironema* or *microspironema pallidum*, discovered by Schaudinn in collaboration with Hoffmann in 1905. It is transmitted usually by sexual contact but may be transferred by accidental extragenital contact with infectious lesions or infected materials such as cups and towels; it may also be transmitted congenitally from parent to child. In ancient writings the disease is confused with other venereal disease, as indicated by the experiments of John Hunter. This view was not abandoned until the early part of the nineteenth century, when the work of Bell and of Ricord demonstrated clearly the separate identity of syphilis and gonorrhea. The history of the disease is obscured by ignorance of its nature and by national prejudice. To-day it is endemic in all parts of the world.

Causative Organism.—Of the names given the organism, the rules of scientific nomenclature favor the adoption of the term *spironema pallidum* but many prefer the name proposed by Schaudinn in later publications, *treponema pallidum* and good usage still permits the original name *spirocheta pallida*. The nomenclature and classification are discussed fully by Noguchi. *Treponema pallidum* is a slender, closely coiled organism about eight micra (3 to 15) in length and about 0.5 micron in transverse diameter. The coils are regular and closely placed; the ends of the organism are pointed and at each end is a short flagellum-like strand. Motility is marked both in rotation and in progression. It does not stain with ordinary anilin dyes and is gram negative. It may be stained by the Giemsa or the Fontana method, or demonstrated either by the dark field illuminator or by rendering the background opaque with India ink. In tissues it is stained by the Levaditi technique or some modification such as that of Warthin. It can be grown in pure culture on the special medium of Noguchi, especially if taken from uncontaminated tissues such as the syphilitic rabbit

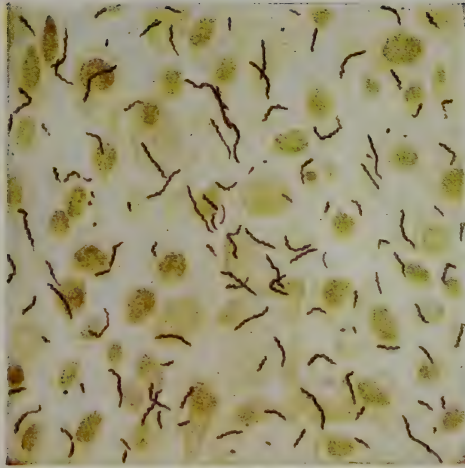


PLATE X—Spirochetes in a chancre of the penis,
stained by the Levaditi technique.



testicle. The organisms are extremely numerous in the liver, lung and other organs of congenital syphilis, are numerous in primary and early secondary lesions of acquired syphilis, but are reduced in number in subsequent stages of the disease.

The organisms divide by longitudinal fission and according to Noguchi those that appear to divide by transverse fission, are simply organisms which have divided by longitudinal fission and are adherent at the ends. Mierowsky believes, as the result of finding small globoid bodies and branching filaments, that multiplication may occur by budding and fructification. Such a cycle, however, is by no means proven. *Treponema pallidum* does not pass porcelain filters, but by the technique of Noguchi may grow through the filter pores.

Studies of the resistance of treponemata to alterations of environment are numerous. According to Noguchi, organisms in culture are more resistant than those freshly removed from tissues. Drying kills them promptly. Although after removal of organisms from infected rabbit testicle motility soon becomes sluggish, yet they remain infective when kept at 37° C. for forty-eight hours and sometimes seventy-two hours. Undisturbed solid cultures live for a year at 37° C. At 15° C. they live four or five months and at 2° C. for about two months. Fluid cultures are less resistant. Closely similar organisms resist direct sunlight for more than four and one-half hours. Temperatures of 50° to 55° C. kill in thirty minutes. Of considerable practical importance is the demonstration by Zinsser and Hopkins that treponemata remain alive on a moist towel at room temperature for more than eleven and one-half hours, and that of Reasoner that soap solutions kill almost immediately. Haythorn and Lacy recovered living organisms from a stillborn, syphilitic fetus twenty-six hours after delivery. Common disinfectants are fatal to the organisms. A series of chemicals used by Bronfenbrenner and Noguchi were from twenty to one hundred times more toxic for the *treponema pallidum* than for the colon bacillus. Chemotherapeutic researches show moderate effectiveness of compounds of mercury but most valuable are the compounds of arsenic, particularly salvarsan, neo-salvarsan and closely related compounds. The arsenic compounds operate *in vitro* but are much more effective *in vivo*.

In early work Noguchi recognized three morphologic varieties, but these are now believed to be due to environmental differences (see Pearce). Noguchi, Nichols, Reasoner and others were of the opinion that certain strains are especially prone to produce disease of the central nervous system. Levaditi and Marie maintain that neurotropic and dermatropic strains are recognizable. Experimental and clinical evidence has been offered both for and against this hypothesis and the best that can be said for it is that it is not yet proven.

Demonstration of Causative Relation.—Syphilis was transmitted to animals by Metchnikoff and Roux in 1903, who produced primary lesions in the chimpanzee by material from early human lesions. Bertarelli in 1906 successfully inoculated rabbits and Parodi in 1907 introduced the method of inoculation of the rabbit's testis. Uhlenhuth and Mulzer, as well as Brown and Pearce, have shown that the rabbit may exhibit primary, secondary and probably tertiary lesions. Noguchi grew the organism in pure culture and with the first few generations of cultures produced clinical syphilis in monkeys, which subsequently responded positively to the Wassermann test. The organism therefore has met the postulates of Koch. It is practically constant in syphilis, can be grown in pure culture, which upon inoculation produces the disease in animals, and is recoverable from the experimental lesions. Slight transient local lesions have been produced in other species such as the guinea pig, dog, sheep and horse, but these are not comparable to the disease as produced in apes and rabbits.

Doubt was thrown on the work with syphilis in rabbits by the discovery that a disease occurs in these animals somewhat like experimental syphilis and caused by *spirocheta cuniculi*. Subsequent studies have shown that the two diseases are distinguishable and the experimental work with syphilis can be accepted (Kolle, Ruppert and Moebus, and Warthin, Buffington and Wanstrom).

Lesions in Man.—It is customary to divide the manifestations of syphilis in man into a primary stage, a secondary stage and a tertiary stage. Formerly

there was described a parasyphilitic or metasyphilitic stage, in which sclerotic lesions, particularly of the central nervous and vascular systems, appear, but now it is known that these lesions are directly attributable to the treponema and are therefore truly syphilitic rather than parasyphilitic. The division into stages is convenient but not always practicable. The primary stage is usually distinctive, but sharp separation between secondary and tertiary stages is sometimes impossible. It is essential to regard syphilis as a disease which shows recurring cycles of manifestations. In the secondary stage several recrudescences may appear, separated by periods of latency. The lesions of the later recrudescences tend to be more destructive and somewhat more deep seated, and it is often difficult to determine whether these lesions should be classed as secondary or tertiary, e.g., the serpiginous skin ulcers and the syphilitic rupia. This stage may also show cycles of recurrence, or may be

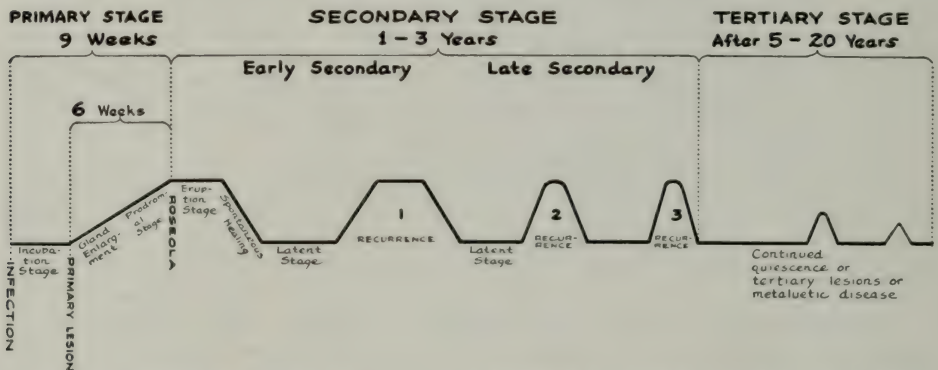


Fig. 107—Diagram to show cyclic development of symptoms and signs in syphilis; the peaks indicate clinical manifestations in general, not necessarily fever. Modified from Kolle and Hetsch, *Die Experimentelle Bakteriologie und die Infektionskrankheiten*, Berlin, 1919.

evidenced simply by the functional deficiency of organs the seat of advanced syphilitic fibrosis.

Infection is usually by sexual contact and the primary lesion, the chancre, is found upon the glans penis or prepuce, upon the labia, vaginal wall or uterine cervix. Chancres of the lip, tongue, tonsil, nipple, finger or other extragenital situation are the result of accidental contamination by towels, drinking and eating utensils, pipes, clothing, etc., innocent kissing, sexual perversions, or may represent accidental infections, as on the hands of physicians and nurses or the breasts of wet-nurses. The period of incubation is from two to five weeks, usually about three weeks. In the vast majority of instances, a chancre appears at the point of inoculation, but cases are on record, as clearly pointed out by Fordyce, in which the disease develops without chancre. Such cases are not to be confused with those in which the chancre is concealed, as in the anterior urethra of males and in the vagina and uterine cervix. After gaining entrance, the organisms are rapidly disseminated, particularly through the lymphatics. In monkeys they are found in the spleen and bone marrow before the primary lesion appears; Brown and Pearce have demonstrated them in the regional lymph nodes of rabbits two days after inoculation in the scrotum.

Gaining access to the regional nodes they pass to other nodes and remain for a long period. In rabbits it is possible to recover organisms from the blood stream from the beginning to the regression of the local lesion, and in some instances, several days before the local reaction appears. Clinically the excision of the chancre does not prevent full development of the disease, and the same is true of excision of the primary testicular lesion in animals. Warthin's work indicates that once the disease is established, the organisms are probably never entirely removed from the body.

Before the development of the primary lesion there is, as has been stated, a period of incubation in which symptoms are absent. After the subsidence of the chancre there is a period of latency, very variable in duration, before secondary lesions occur. After the secondary stage a period of latency is observed which may be short or may last over many years. Tertiary lesions may occur and subside, particularly when treated, only to recur at some later time. Fibrosis and sclerosis of later syphilis progress in spite of clinical and even immunological evidence indicating quiescence of the disease.

The **primary lesion** is the hard chancre or Hunterian chancre or true chancre and is to be differentiated from the soft chancre or chancroid, ascribed to an entirely different organism. The typical Hunterian chancre begins as either an acuminate or flat papule, firm, slightly reddened and painless. The induration may extend beyond the margin and upon palpation feel like



Fig. 108—Photograph of chancre of reflected layer of prepuce. From White and Martin's *Genito-Urinary Surgery*.

a subcutaneous "button." Owing to a superficial necrosis, ulceration appears comparatively early but may be preceded by the formation of a vesicle. As usually observed, the chancre is a single ulcer varying in diameter from a few millimeters to more than a centimeter, with a red moist base sometimes covered with a crust of dried exudate, and surrounded by an elevated dense margin, the remnant of the original papule. As the lesion becomes older the marginal density or induration may extend several millimeters beyond the edge of the ulcer. Shortly after the appearance of the chancre, the regional lymph nodes are enlarged and firm, painless and rarely tender. Histologically, the fully developed chancre is a generally spherical mass of mononuclear cells, provided with a variable number of new capillaries. It is situated in the corium but may extend more deeply; involvement of the epiderm is principally in the formation of the ulcer. In the stage of ulceration, superficial necrosis is observed with slight acute inflammation at the base. Secondary infection of

the ulcer, with pronounced acute inflammation may obscure the picture histologically, grossly and clinically. The cells of the chancre are principally lymphoid cells with a number of endothelial cells. Multinuclear giant cells, with vesicular centrally disposed nuclei, are occasionally encountered. The investigations of Fordyce and of Brown indicate an early lesion of the smaller blood vessels and capillaries. Brown finds that as soon as the organisms proliferate they are grouped about the capillaries, probably in association with injury of the endothelium (personal communication). There is slight exudation of leucocytes accompanied by local necrosis, rapidly followed by infiltration of



FIG. 109.—Microscopic appearance of margin of chancre. The corium is diffusely infiltrated with mononuclear cells. The lesion has existed for some time as indicated by the well marked epithelial proliferation at the margin of the ulcer.

lymphoid cells in mantle form about the preëxisting and new vessels, which soon spreads into the surrounding tissues to form a solid mass of cells. The vascular endothelium swells and probably proliferates. As the condition progresses, fibroblasts may be found intermingled with the other cells, and in the later stages of the lesion, it is not uncommon to find that the smaller vessels within the lesion or near its margin show moderate or marked fibrotic thickening of their walls. Special staining demonstrates numerous organisms both within the cells and between them, and by examination of stained smears they can be found in the thin fluid upon the surface of the ulcer. The fibroblasts rarely produce the formation of significant amounts of connective tissue, and hence the chancre heals with very slight scar formation save for that due to the secondarily infected ulcerated surface.

The secondary stage of syphilis is characterized by lesions of the skin and mucous membranes and enlargement of lymph nodes. The skin lesions may be macular erythematous, maculopapular, papular and even pustular. The macular eruptions show histologically only dilatation of the small vessels of the papillary bodies and adjacent corium, sometimes with slight perivascular infiltration of lymphocytes and plasma cells. In the papular varieties the

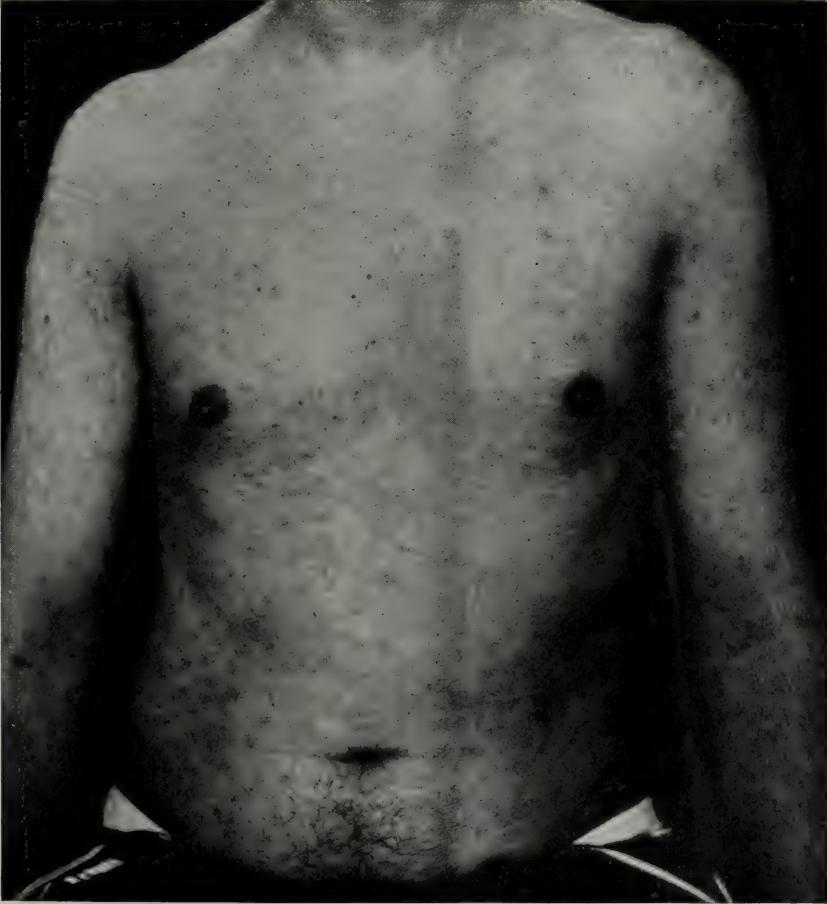


FIG. 110—Photograph of erythematous syphilide, secondary stage of syphilis. From Hartzell, Diseases of the Skin.

lesion is a circumscribed mass of lymphocytes, plasma cells and endothelial cells with a varying number of fibroblasts. According to Fordyce, the pustular forms are due to secondary pyogenic infection and consequently show acute suppurative inflammation. Mucous patches appear in the mucous membranes of the mouth, vagina and anal margin. These are at first flat papules but rapidly ulcerate to form shallow flat ulcers, well defined, reddened at the base and with slightly elevated margins. Microscopically, the lesion of the corium is like that of the papular skin lesions, although not so sharply circumscribed, and in the depths shows a well marked perivascular distribution of the cells.

The epithelium is at first swollen, then becomes necrotic and exfoliates. The exposed surface is essentially granulation tissue and is resistant to secondary infection. The lymph nodes are moderately enlarged, easily palpable, firm and usually neither painful nor tender. Histologically, there is subacute or chronic hyperplasia. The germinal follicles may be enlarged and active, the sinuses show a moderate endothelial hyperplasia and fibrosis is usually pronounced. Pain or tenderness in the periosteum of the long bones, especially of the tibia, is common and is due to a mild subacute periostitis. Areas of baldness, or alopecia, may result from mild cutaneous lesions of the scalp.

The third stage of syphilis, as now understood, includes the entire period of



Fig. 111—Photograph of miliary pustular syphiloderma. From Hartzell, *Diseases of the Skin*.

the disease following the secondary stage. There may be a period of clinical latency following the subsidence of secondary lesions, but that the disease fails to show definite anatomical lesions during this period, is doubtful. The third stage was formerly identified by the appearance of the gumma, but the studies of Warthin indicate that the gumma is an incident of tertiary syphilis, and that the predominant lesion is a progressive fibrosis of most of the internal viscera. He believes "that the gumma is not the type lesion of late or latent syphilis, and that the viscera are involved in all cases of latent syphilis, not by gummatous processes, but

by specific inflammatory processes, eventually fibrosis, usually mild in character, but acquiring pathologic importance because of their progressive character."

Although the primary and secondary lesions of syphilis are granulomatous in character the gumma is typically so. It may appear in any tissue in the body. The classical gumma is a solitary, fairly large nodule without secondary or daughter lesions. It may attain a diameter of several centimeters but usually averages about 1 to 1.5 cm. Nevertheless, small gummata of microscopic or miliary size may occur and these are usually multiple. The solitary gumma is a relatively firm, elastic structure surrounded by a granulomatous cell mass and fibrous connective tissue. Upon cross section the center of the lesion is a slightly gelatinous, elastic, somewhat hyalinized necrotic mass. The consistency is that of fairly firm rubber and from this is derived the name,

gumma. The central necrosis may also be caseous or mucinous in character. Histologically, the lesion very closely resembles the tubercle. The central necrotic mass may be hyaline microscopically, but more frequently, even though grossly hyaline, is finely granular as in caseous or coagulation necrosis. Around the necrotic area is a rim of cells, principally endothelial cells and lymphocytes. As a rule, the lymphocytes far outnumber the endothelial cells. Giant cells similar to those of the tubercle are sometimes present but as a rule are not numerous, and usually are entirely absent. Intermingled with the layer of lymphocytes is found a proliferation of fibroblasts or of adult connective tissue, which contains numerous capillaries. The vascularization of the gumma often extends well down toward the necrotic area, and in this respect the gumma differs markedly from the tubercle. In the later stages of the lesion, cicatrization or encapsulation is likely to be marked and the fibrosis may extend widely into the surrounding tissue. Not infrequently the blood vessels



Fig. 112—Photograph of tertiary syphilide of skin. Patient subsequently completely relieved by specific treatment. Patient of Dr. H. N. Cole.

of the neighborhood show distinct fibrous thickening of their walls. Special stains may show the treponemata in small numbers, but usually they escape observation. Gummata in the skin, or mucous membrane, may show deep ulceration. Hemorrhage from the ulcerated lesion may lead to serious anemia and sometimes death. Sometimes marginal thrombosis of vessels occurs so that the lesions progressively extend to form large ulcers, which are likely to be chronic and progressive so as to produce the so-called serpiginous ulcers. Miliary gummata may appear in considerable numbers in the skin and are not infrequent in the media of the aorta.

Throughout late syphilis there is a slowly progressive "irritative or inflammatory process, usually mild in degree, characterized by lymphocytic and plasma cell infiltrations in the stroma" of most of the viscera, "particularly about the blood vessels and lymphatics, slight tissue proliferations, eventually fibrosis, and atrophy or degeneration of the parenchyma" (Warthin). These changes require years for their development and are due to the presence in the tissues of treponemata. Grossly, the more advanced lesions are recognizable as small areas, but the fibrosis usually is of only microscopic

size. The nervous system, heart, aorta, pancreas, adrenals, testis are likely to be affected, and morphologically similar lesions are found in the kidney and other organs.

In the central nervous system the pia-arachnoid may show diffuse or localized thickening, the latter being associated with fibrosis of the walls or complete fibrotic occlusion of the meningeal vessels. In the nervous tissue there may be focal areas of gliosis or perivascular infiltrates of lymphocytes



FIG. 113—Multiple gummata of the auricle of the heart.

and plasma cells. More extensive gliosis occurs in cases of paresis, associated with cortical atrophy; the areas are irregularly distributed in cerebrospinal syphilis and affect the posterior columns in tabes dorsalis or locomotor ataxia, with associated destruction of cells and neuraxons. It is possible that these more serious lesions represent progression from the minor lesions.

The heart may or may not show fibrosis grossly. Microscopically there are perivascular infiltrates in the myocardium, especially near the endocardium. This fibrosis is usually patchy but may be diffuse. The local lesion may consist of small accumulations of lymphocytes and plasma cells, with slight fibrosis

between the muscle fibers, or larger accumulations about larger vessels, and may approach in size miliary gummata. They do not show the necrosis, the vascularization, nor the giant cells of gumma. The muscle may show hypertrophy, atrophy, fatty degeneration or even necrosis. The endocardium is not likely to be affected save for the aortic valves, which not infrequently are the seat of sclerosis. The aorta in syphilis may show a simple intimal sclerosis, in which the media shows microscopically mild perivascular cellular infiltration, or the vessel may be the seat of the grossly recognizable syphilitic mesaortitis. This is usually limited to the arch of the aorta but occasionally is more extensive. The intima is irregularly thickened and shows hyalinization to a greater degree than atheroma or calcification. The intima shows numerous depressed lines, which produce wrinkling or stellate figures. Cicatricial areas

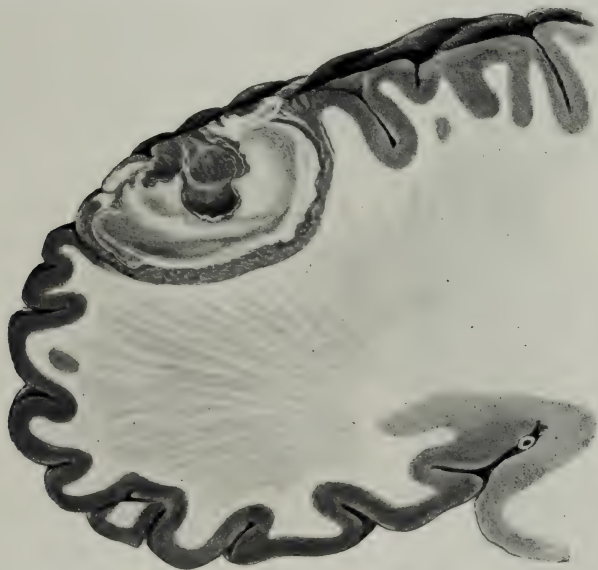


Fig. 114—Gumma of the cerebrum.

in the media are sometimes visible to the naked eye. Microscopically, the lesions are situated about the vasa vasorum in the form of infiltrates of lymphocytes and plasma cells; the muscular and elastic laminae are interrupted by these lesions. In the advanced stages, fibrosis is pronounced and strands of dense fibrous tissue extend to the lines of depression in the intima, which are produced by the contraction of the fibrous tissue. The peripheral arteries may show similar changes. Dilatation and aneurysm formation are common in syphilitic aortitis and also occur in syphilis of the smaller arteries.

The liver may show localized fibrosis of the same general nature as that elsewhere, perilobular fibrosis and atrophic cirrhosis, or it may become the *hepar lobatum* which is grossly indicative of syphilis. The lobated liver is produced by the contraction of masses of fibrous tissue which lead to lines of depression in the surface and the formation of pseudolobes. The bands of connective tissue often radiate from gummata in the liver, but occasionally

no gumma is found. The pancreas frequently shows irregularly disposed interstitial fibrosis and an associated atrophy of the parenchyma.

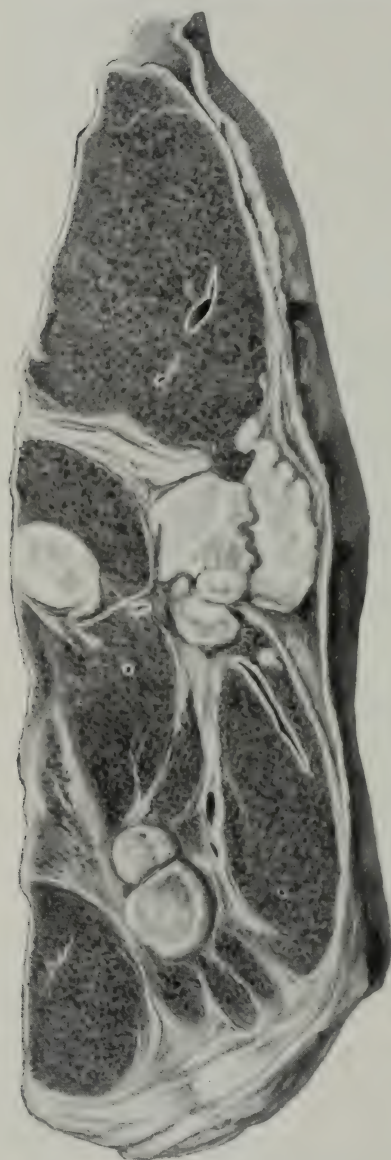
The testis is almost constantly the seat either of cellular infiltrates or of fibrosis of the interstitial substance, which may be general or focalized and associated with fibrosis of the basement membrane and decreased spermatogenesis. The kidney often shows more or less marked chronic interstitial nephritis.

Warthin has found treponemata in the earlier cellular infiltrates and in the subsequent stages until dense cicatricial tissue develops, when they are no longer demonstrable. Warthin states that "the specific inflammatory lesions of spirochete localization have been found in the myo-, endo-, and pericardium, the aorta, pulmonary and other large arteries, nervous system, liver, pancreas, adrenals, testis, prostate, pre-vertebral and mesenteric tissues." Treponemata have been demonstrated by numerous others in the aorta; Noguchi and others have found them also in the lesions of paresis.

Congenital Syphilis.—Syphilis is not hereditary, but the birth of children the victims of the disease indicates that it is congenital. Treponemata are found in the placentas of syphilitic mothers and directly infect the embryo or fetus. The organisms may be found in the semen of syphilitics, but it is unlikely that an ovum invaded by the organisms could multiply because it is known that the disturbance of a single blastomere in the lower vertebrates leads to arrest of development or production of malformations; if this be true of lower vertebrates with their high power of regeneration, the effect would probably be much more severe in the higher mammals and man. Infection of the embryo probably only occurs by infection of the mother at or preceding the time of conception.

FIG. 115—Gross section of multiple gummata of liver, with heavy bands of fibrous connective tissue radiating through the organ.

Hata found that of syphilitic women married for at least three years only 60 per cent. were impregnated. As a result of the pregnancies there were 28 per cent. abortions, 42 per cent. living infants which died within two years of birth and 30 per cent. of living children which sur-



vived for two years or more. He states that many of the surviving children are defective or die young, owing to syphilis. Congenital syphilitics may live to adult life with few or no signs or symptoms of the disease. Their children

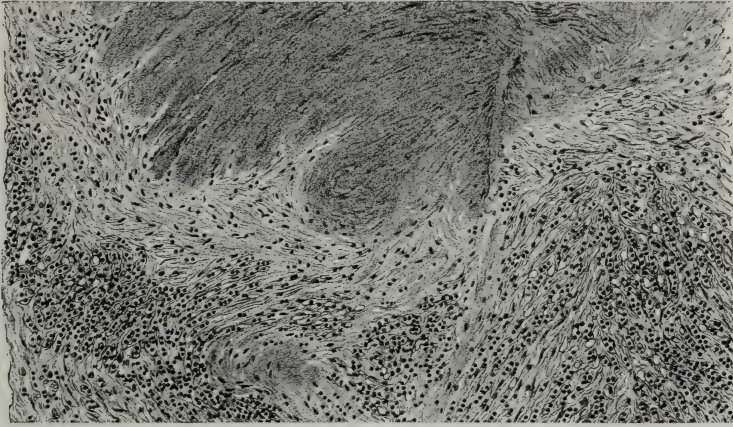


Fig. 116—Section of gumma. Note necrosis above. In margin of necrotic area are a few epithelioid cells. There is a rich infiltrate of lymphoid cells in a well vascularized mass of granulation.

may show obvious syphilis. There are records of syphilis transmitted through three generations.

Among the skin lesions of stillborn congenital syphilitics, the more important are bullæ of the palms of the hands and soles of the feet, and general maceration of the skin. The internal viscera may or may not be enlarged but microscopically show faulty development. The kidney, liver, pancreas, and the lung are dense, relatively fibrous organs. On histological examination, however, it is found that this density is not due to an increase in fibrous connective tissue, but rather to a failure of development on the part of ingrowing epithelium or other structure which fails to displace the original mesoblastic tissue. Thus, the alveoli of the lungs are not fully developed and are separated from one another by masses of tissue made up particularly of small round cells resembling very closely those of the mesoblast ("white pneumonia"). The liver is likely to show large, thick, perilobular spaces filled with connective tissue and the same types of cells as are seen in the lung. This



FIG. 117—Syphilitic scars in epiglottis.

may show obvious syphilis. There are records of syphilis transmitted through three generations.

may be true not only of the perilobular connective tissue but the cells may be present in fairly large numbers between the liver cords. The development of the pancreas is similarly delayed so that between small and imperfectly developed acini the mesoblastic tissues or its descendants remain undifferentiated. In the kidney the same mesoblastic remnants are found. Bone formation is also delayed so that the development of the diaphysis is particularly affected. The gross examination of the ends of long bones shows between

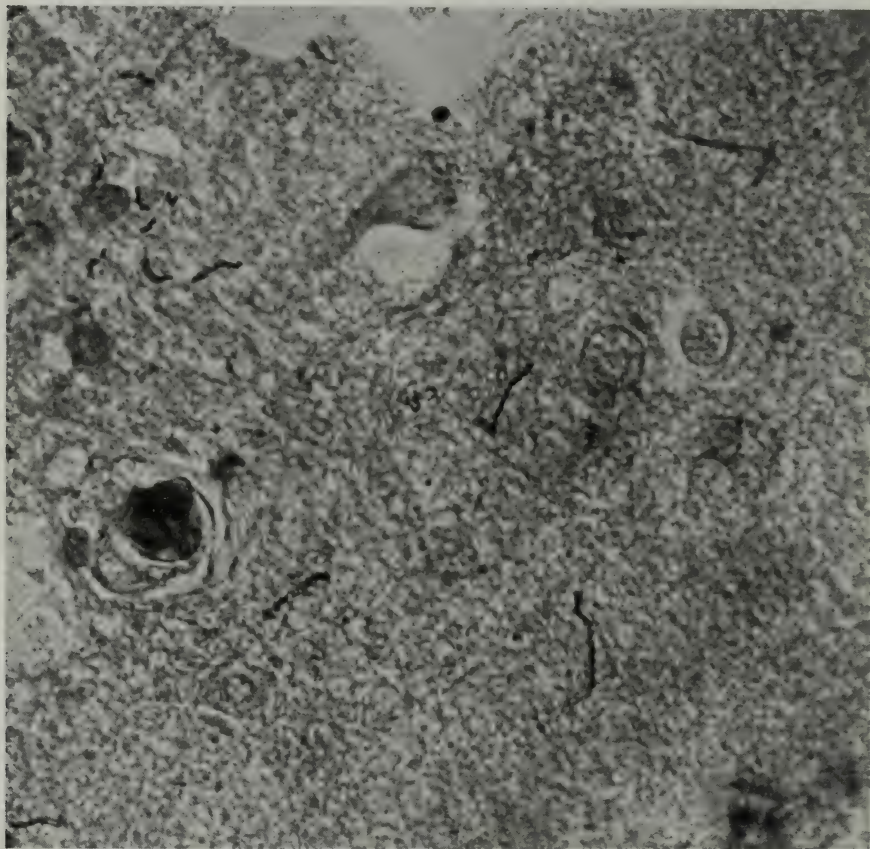


FIG. 118—Spirochetes in brain of paresis. From Noguchi and Moore, *Jour. Exp. Med.*

the diaphysis and the epiphysis a thick, yellow, irregular line. This is in contrast to the sharp, narrow white line that appears normally. Histologically, the development of the trabeculae in the primary spongiosa, instead of proceeding regularly with the formation of parallel columns of tissue, proceeds irregularly so that there is an alteration of the normal parallelism. The viscera are likely to be crowded with treponemata.

Infants born alive are likely to be undersized, wizened infants with widely open fontanelles; the angles of the mouth show radiating linear scars, the syphilitic ragades, and they may be the victims of a syphilitic rhinitis or "snuffles." Sometimes infants are born apparently healthy and at about

the second month exhibit snuffles, ragades, not infrequently discharge from the ears and deafness. Ulcerations of the nose with necrosis of the septal bones may lead to perforation of the septum and to dropping of the bridge of nose, the so-called saddle nose. Cutaneous lesions and mucous patches similar to those of acquired syphilis may occur. The bone ends, liver and spleen are usually enlarged. These cases frequently die and show visceral lesions similar to but of less marked degree than those of the stillborn. *Treponemata* are not so numerous in the lesions. Teething is likely to be delayed. When the teeth of the second dentition appear they are of the Hutchinson type, peg shaped and with a circular indentation of the cutting edge which is the large arc of a small circle. The disease may become quiescent after the early outbreak, to appear again at puberty or later. Iritis and chronic interstitial keratitis may appear in early infancy but the keratitis is more common at puberty or later. Hutchinson's triad of congenital syphilis includes malformation of the teeth, keratitis and deafness. Gumma formation is not common in congenital syphilis but is sometimes seen in the stillborn and less often in the living infants and children.

Immunity in Syphilis.—A consideration of this topic must distinguish between manifestations *in vitro* and those *in vivo*. An important question is as to whether or not an attack of the disease renders the patient immune to subsequent attacks. Formerly it was assumed that reinfections are uncommon, that supposedly cured patients are immune. By the use of the Wassermann test it was found that many patients clinically free from symptoms were still victims of the disease. The studies of Warthin indicate that, although the Wassermann test may be negative in late syphilis, nevertheless the patient may harbor spirochetes. Many authorities doubt that syphilis is ever cured. Kolle and Hetsch, however, state that more than one hundred well authenticated second attacks of syphilis are reported in the literature, and it is probable that these represent new infections after a cure. If this be true, it is apparent that syphilis does not lead to a lasting immunity. Pearce and Brown have been able to establish a superinfection in rabbits treated for, but not cured of, a preceding infection. A second infection does not necessarily indicate the cure of the first infection; it may, however, have some bearing upon variations in resistance during the course of an infection. Such reinfection is not readily established and the animals are more or less refractory to it. Chesney and Kemp, as the result of extensive experimental studies, believe that this refractory stage is due to an acquired immunity rather than to persistence of foci of living *treponemata* in the body. Colles' or Colles-Baumes' law to the effect that mothers who give birth to syphilitic children and who give no evidence of syphilis, are immune to the disease, has been abandoned since it has been shown that such mothers in the vast majority of instances react positively to the Wassermann test and are the victims of latent syphilis. Profeta's law that children of a syphilitic mother are immune to the acquired disease is no longer tenable; such children as do not exhibit syphilis are resistant because they are victims of the disease, even though it be latent.

The general reaction of the body to *treponema pallidum* is more nearly like that to protozoa than to bacteria. The primary defenses of the organism have some influence on the subsequent disease, since Brown and Pearce have shown

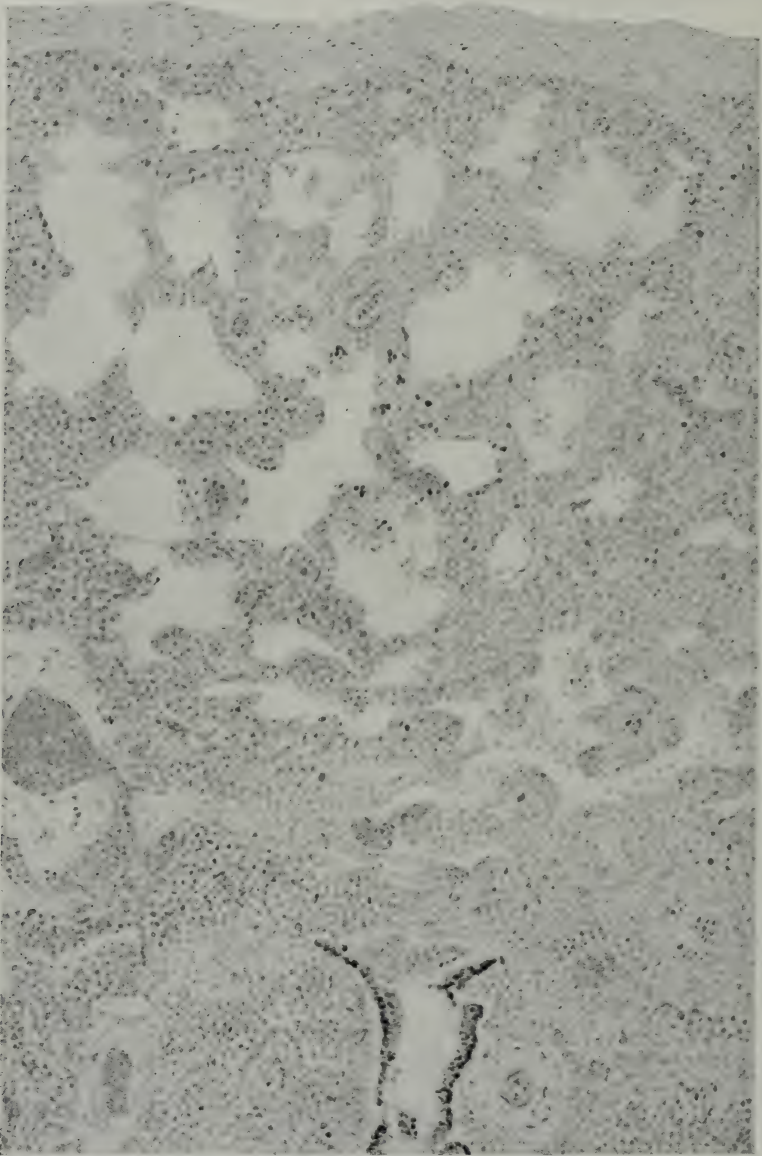


FIG. 119—Congenital syphilis of lung (pneumonia alba) showing thick alveolar walls.

that removal of the primary lesion in the rabbit or depression of the primary reaction by drugs, favors more rapid development of subsequent generalized manifestations of disease. The presence of syphilis in the body leads to an alteration of the tissues and fluids which apparently represents an unstable balance between resistance and hypersusceptibility, but a high degree of

immunity does not seem to occur. By good technique and proper dosage, Finger and Landsteiner found that it is possible to inoculate spirochetes locally at almost any stage of the disease, but the incubation is short, the lesions are less pronounced and regress more rapidly. The lesions resemble those of the stage of the disease during which inoculation takes place. Thus, in the primary stage a chancre-like lesion is produced, in the secondary stage a papular skin lesion, in the tertiary stage a destructive lesion resembling the gumma. The cycles of syphilis show periods of active lesion alternating with periods of latency. The explanation of these cycles is at this time largely hypothetical, since it is evidently difficult to work with concrete manifesta-

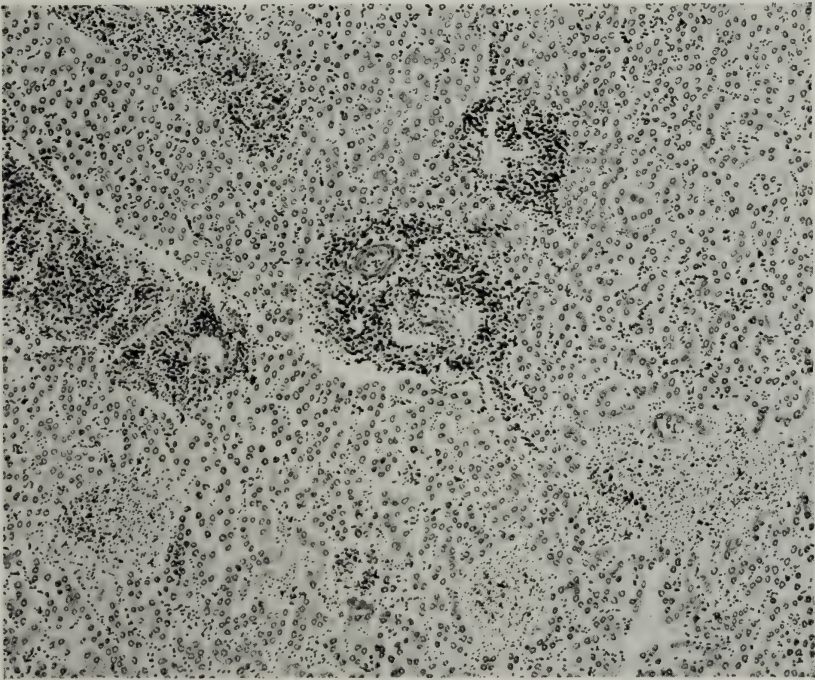


Fig. 120—Congenital syphilis of liver, showing cellular infiltrate in peribulbar connective tissue and foci of necrosis in parenchyma.

tions of immune bodies or of susceptibility. In the primary stage there is probably a rapid increase in resistance of the body, since reinoculation is difficult and multiple chancres rare. The subsequent period of latency shows little resistance and may represent even depressed resistance or a "negative phase." This is probably a true incubation period of the disease, but not of generalization of the organisms since they spread rapidly from the primary lesion. Only after the development of the secondaries does a true resistance develop, as represented in the next period of latency. In the primary and early secondary lesions the organisms are numerous, progressively decreasing in number with subsequent lesions. The later lesions, however, with smaller numbers of organisms, are progressively more and more destructive. This is assumed to be due to an alteration of tissue reactivity, a state of allergy or a

true hypersensitiveness. Even with hypersensitiveness, the activity of the disease is presumably sufficient to lead again to resistance, with latency followed by new hypersensitiveness as the resistance gradually disappears. In the stage of gumma formation, only a few organisms are associated with the marked tissue destruction and severe local reaction. It is possible, however, that the number of organisms may be so small that the gumma is not formed; the reaction then is solely in the form of the low grade inflammation and fibrosis described by Warthin. That these cycles are due to alterations of the treponemata is unlikely, since they are equally infective at all stages of the disease.

Such immune processes as can be demonstrated *in vitro* have been carefully studied. Attempts have been made to protect animals by multiple injections of living culture treponemata, but in spite of the production of demonstrable immune bodies, the animals are not resistant to inoculations of virulent organisms. Vaccination with dead organisms was equally unsuccessful. Agglutinins have been produced in rabbits and sheep, usually of fairly high titre; Zinsser and his coworkers report one serum with a titre of 1-4000. The agglutinins operate upon culture treponemata, but are relatively inactive against virulent organisms. The serum of human syphilitics and syphilitic animals contains agglutinins for culture treponemata, and apparently also for virulent treponemata, in such small amounts as to be demonstrable only with some difficulty and in a small proportion of patients. Kolmer and his collaborators report low titre agglutinins in 84 per cent. of tertiary and latent lues, but admit that the method is not yet practicable as a diagnostic test. Landsteiner and Mucha found the serum of patients weak in agglutinins, but demonstrated greater agglutinating power in the tissue juices from cutaneous papules and sclerotic areas; this they suggest may be an indication of local agglutinin production. Zinsser, Hopkins and McBurney, as well as Noguchi and Akatsu, found that the agglutinins from immunized animals show pronounced group reactions with closely associated organisms. The immune serum exhibits definite treponemicidal activity upon culture treponemata but not upon virulent organisms. Heating at 56° C. for one-half hour destroys the treponemicidal activity, and addition of complement restores it; the action is therefore similar to that of bactericidal immune bodies. Kolmer and Broadwell were unable to demonstrate treponemicidal activity on the part of serum from human syphilitics. Low titre opsonins occur in immune animal sera and are augmented in activity by the addition of complement.

By the use of culture treponemata in suspension, Noguchi was able to demonstrate an intracutaneous reaction in syphilis, the so-called luetin test. This is present in a large number of luetic patients, but is less constant than the positive Wassermann test. False positives interpose considerable difficulty of interpretation. That this test is an indication of local hypersusceptibility seems probable, but it does not follow in intensity the cyclic evolution of the disease. The repeated injection of culture treponemata in animals is followed by positive luetin tests, but such animals are not immune to inoculation with virulent organisms; the test is therefore not an indication of immunity.

The use of treponemata as antigen in complement fixation tests demonstrates the presence, in immunized animals and in human lues, of "fixing bodies," but reactions are not sufficiently constant to justify the use of this type of complement fixation as a diagnostic test.

Neither in immunized animals nor in human syphilis is there any parallelism between agglutination, treponemicidal activity, positive luetin tests, specific complement fixation tests and the Wassermann test. Inoculation syphilis in animals and syphilis in man stimulates little antibody formation. Local cellular reactions to inoculation are of importance, as has been mentioned, but whether this is simply an inflammatory defense or due to local antibody production is problematical.

The Wassermann Test.—This is not considered as an immune reaction in the sense indicated above. The antigens ordinarily employed are not antigens in the strict biological sense, but rather finely suspended colloidal emulsions of lipoids, particularly lecithin and lipoids of the diaminophosphatid group, as well as fatty acids and certain proteins or protein fractions. The "fixing body" or "amboceptor" of the luetic serum is a substance apparently closely related to the globulins, especially the euglobulins; the globulins are known to be increased in syphilitic blood and spinal fluid. According to Wells "a favorite interpretation of the Wassermann reaction, which seems to harmonize with the facts, is that there is a precipitation of serum globulin by the lipoidal colloids of the antigen and adsorption of the complement by this precipitate."

The Wassermann test is positive in a large proportion of all syphilitics. Craig found 86.2 per cent. positive in 4658 cases diagnosed clinically as syphilis, and it must be remembered that there is at least a small factor of error in the clinical diagnosis. It is therefore apparent that the presence of a syphilitic infection leads to some change in the body, by which a substance is elaborated capable of fixing complement in the presence of the antigen. That this substance is an immune body is not as yet proven. The most satisfactory antigen is not a biologically specific body, i.e., not the *treponema pallidum*. The test shows a greater percentage of positive results in secondary syphilis, i.e., during the most active stages of the disease; therefore, it is not indicative of resistance nor is the "fixing body" indicative of immunity. As pointed out above, the Wassermann test does not parallel the presence of agglutinins, treponemicidal substances, the luetin test nor specific complement fixation. The Wassermann test cannot be regarded as an indication of immunity or lack of it. It is the result of changes which occur in the body as the result of infection, referable rather to alterations in the body fluids than to production of immune bodies.

The value of the Wassermann test as an aid in the clinical diagnosis of syphilis is not altered by any speculations as to its nature. Although not specific in the biological sense, it is positive in other diseases. Craig found the test positive in eleven cases (0.4 per cent.) of 2643 examined, including four cases of malaria, three of tuberculosis, (two of which ultimately gave a clinical history of syphilis), three cases of pityriasis rosea and one case in which the

diagnosis was not established. Careful study of malaria has finally indicated that the disease itself does not give a positive Wassermann and it seems probable that the malaria patients in Craig's statistics were victims also of syphilis. Excluding all the malarial cases and two of the tuberculous cases the percentage is reduced to less than 0.2 per cent. It is possible that diseases other than syphilis may produce those changes in the blood, which lead to fixation of syphilitic antigen and complement; among those are occasional cases of leprosy, scarlatina, trypanosomiasis and certain skin diseases. It is extremely difficult to exclude syphilis in these cases, either because of ignorance of infection on the part of the patient, or deception. In contrast with the figures in normals and diseases other than syphilis, the following figures taken from Craig's work indicate the results of a single test on each of 5600 patients diagnosed clinically as syphilitic.

	Number of cases	Positive	Per cent.
Primary syphilis	1080	970	89.8
Secondary syphilis	2217	2132	96.1
Tertiary syphilis	728	633	87.4
Latent syphilis	1525	1039	68.1
Congenital syphilis	28	25	82.2
Parasyphilis	22	15	68.1
Totals	5600	4814	81.9

Criticism has been directed against the test because of the fact that results do not always agree with clinical findings, and because of differences in results upon the same serum in different laboratories. It must be admitted that the factors of error in the test are numerous. Discrepancies in reports from different laboratories may, in part, be due to inherent faults in the test, to faults in technic, to faults in selection of materials and to insufficient training of the worker. The older literature contains serious criticisms of the test, as for example the papers of Wolbart and of Uhle and Mackinney. Under the direction of the Medical Research Committee of Great Britain in 1918, the results obtained independently by Dr. C. H. Browning, Dr. J. McIntosh and Col. L. W. Harrison upon the same specimens are in very close agreement. More recently Solomon has analyzed the results of 3000 tests carried out in two different laboratories by skilled workers, Dr. Hinton and Dr. Castleman. There was complete agreement of results in 93.44 per cent. of this large series of tests. This study demonstrates that with modern methods and skillful performance of the test, results are highly dependable.

Other Tests.—Certain modifications of the Wassermann test have improved it and other modifications have no demonstrated value. The "luetin" reaction has little or no clinical value in spite of its great interest. No precipitin tests have been devised which completely replace the Wassermann test, but where the Wassermann cannot be satisfactorily carried out, the Kahn precipitin test is an excellent substitute.

YAWS OR FRAMBESIA TROPICA

This disease is confined almost entirely to tropical and subtropical countries. Although it resembles syphilis in some of its clinical manifestations, it is almost entirely a disease of the skin and rarely of the mucous membranes, is not likely to be transmitted by sexual contact, and has a fairly strict geographic distribution. The presence of the one disease does not confer immunity against the other. Yaws is caused by the *treponema pertenue*, first observed by Castellani in 1905. Morphologically *treponema pertenue* resembles *treponema pallidum* very closely, but the coils of the former are not so close or regular, the body is somewhat thicker and the ends are more likely to be hooked or coiled.

The incubation period is variable but is approximately two to four weeks. The disease is somewhat cyclic in course and is said to have three stages. The primary lesion is usually on some exposed part such as leg, ankle, foot, forearm or hand, and it is probable that trauma provides the portal of entry. A slowly growing papule appears in the skin, which shows a moist yellow secretion, tends to become encrusted and shows under the crust an ulcer with granulomatous base. This may extend so as to produce a large, moderately erosive ulcer several centimeters in diameter, and heals either before or after the secondary lesions appear. The secondary stage appears in from one to three months after the primary and shows an eruption of papules over a large part of the body surface, which sometimes ulcerate and coalesce to form large lesions. These clear up and recur after variable intervals, the recurrences being less widespread. The palms and soles may show in the late secondaries a psoriasis-like lesion resembling that of syphilis, and on the soles there may be deep seated nodules with circumvallate ulceration (clavus). The nodule may be extruded leaving a deep ulcer. Lymph node enlargement is common and persistent. In the third stage, gummatous lesions appear, which may ulcerate deeply and produce great deformity. Bones may be involved but deep visceral lesions are practically never found. The primary and secondary lesions do not differ materially and are well described by Moss and Bigelow. "In the frambesic papules the surface epithelium is greatly thickened and numerous elongated downgrowths are seen. In patches the epithelial cells are swollen, vacuolated and degenerating. Circumscribed areas contain polymorphonuclear leucocytes. The layers near the corium are almost normal, but the corium itself is edematous. There is a diffuse, cellular infiltration consisting of polymorphonuclear leucocytes, large and small mononuclears, eosinophiles, plasma cells, mast cells, connective tissue cells and some extravasated erythrocytes." The organisms are found principally in small nests in the epiderm, but may also be found in the perivascular connective tissue of the corium. The *treponemata* disappear after administration of neosalvarsan and the lesions heal rapidly (Goodpasture).

It seems probable that the secondary and tertiary lesions are due to localization of *treponemata* from the blood and that the disease at some period is septicemic.

Experimentally yaws can be transmitted to apes and to the testis of the rabbit, and the organism can be recovered from the lesions. The organism has been grown in pure culture and upon inoculation produces lesions in the rabbit's testis. There is, therefore, little doubt as to its causative relation. The work of Nichols and of Craig and Nichols shows that the serum of syphilitic patients gives crossed reactions with antigens made of pure cultures of *treponema pertenue*, but the reaction is not so strongly nor so frequently positive as with syphilitic antigens. Syphilis of the rabbit does not protect against yaws and vice versa. The Wassermann test is positive in a large percentage of victims of yaws and probably depends more on the crossed reaction than on the coincident presence of syphilis.

ACTINOMYCOSIS

Introduction.—Actinomycosis is a subacute or chronic inflammatory process, leading to suppuration and the formation of granulation tissue, from which pus may be collected containing characteristic, small, white or brownish-white masses, the "sulphur granules" or actinomyces "drusen." It occurs most commonly in cattle and swine as "lumpy jaw," "big jaw" or "wooden tongue."

The causative organism is the actinomyces *bovis* Harz, a member of the order of higher bacteria, actinomycetales, which show long filamentous forms with true branching. The biology of this organism has been studied in this country particularly by J. H. Wright, Waksman, Buchanan and others. Actinomyces *bovis* Harz is a facultative anaërobe, which grows well on ordinary media; it is slightly hemolytic and proteolytic; by careful technique, especially with the Weigert modification, it is gram positive. In cultures which contain animal material, terminal filaments may exhibit a sort of sheath which is gram negative, and probably a transformation or degeneration product rather than a capsule. On inorganic media aerial hyphæ may be produced. It forms neither spores nor conidia. The sulphur granules or "drusen" are masses of the threads of actinomyces. If pressed between glass slides, there is seen a central tangle of threads and in the margin a radiating palisade of thread terminals, usually covered by a transformation hyaline product giving the termini a club-shaped appearance. The clubs are not invariably present. A closely similar organism, actinomyces *Israeli* occurs in man, produces identical lesions, and is to be differentiated chiefly because it is an obligate anaërobe. Numerous other members of the family of actinomycetaceæ are known, some pathogenic for man and animals, some for vegetables and some non-pathogenic. Studies of the effects of drying, sunlight, heat and disinfectants, upon cultures indicates that the resistance of the organism is high, probably as great as, or even greater, than that of the tubercle bacillus.

The Disease in Animals.—In addition to cattle and man, the disease has been reported in swine, horse, sheep, ass, deer, elephant, dog and cat. The primary lesion is in the alimentary canal, jaw, cheek, pharynx, tongue, and intestinal canal, particularly the ileocecal junction. It may also affect the skin. From the primary site, other structures may be affected, as liver, lung, brain or other viscus. Lymph nodes may be enlarged as the result of an inflammatory hyperplasia but rarely by the disease itself. Dissemination appears to follow invasion of blood vessels large enough to carry the organism rather than by the small lymphatic vessels.

Transmission of the Disease.—Experimentally the disease may be produced, but does not show the progressive character of the non-experimental disease. The organisms must be implanted in order to lead to disease, and it is

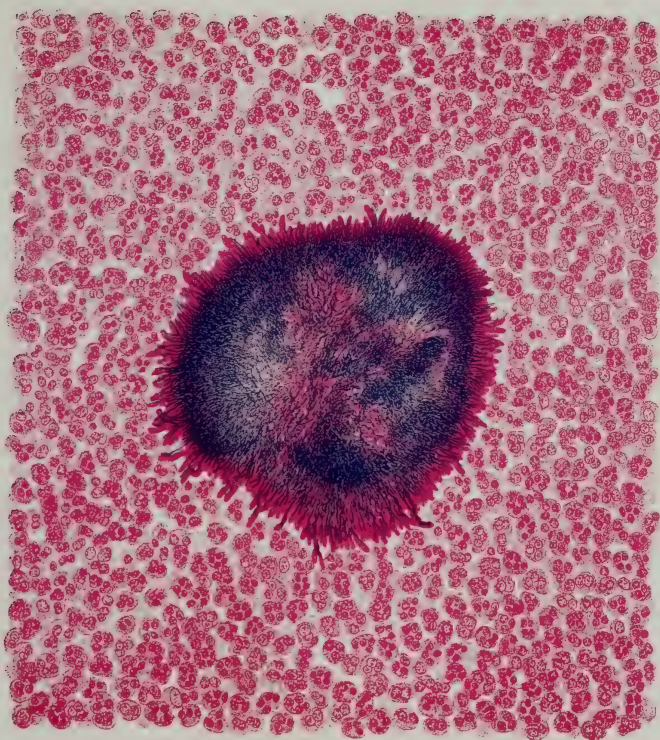
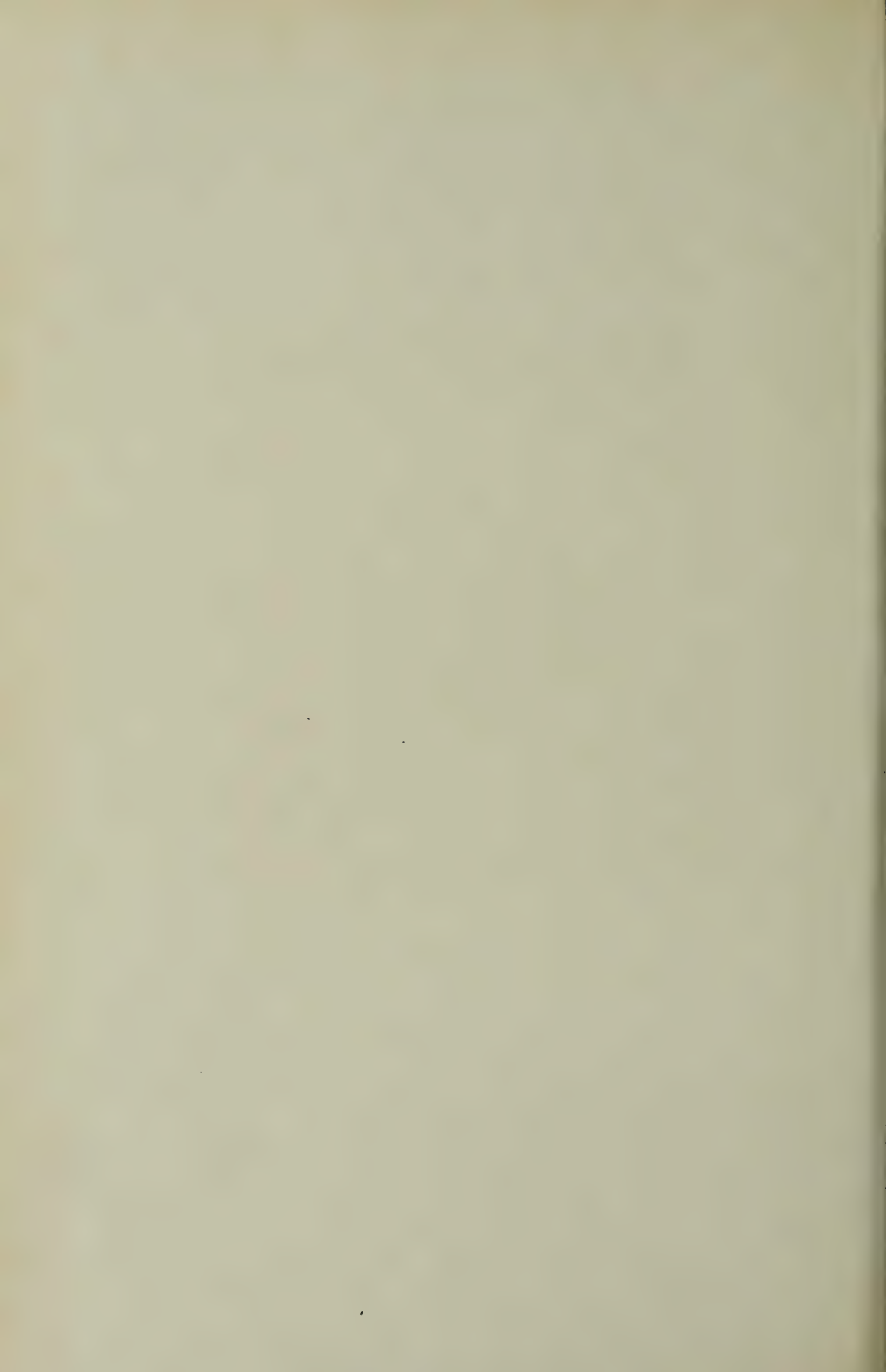


PLATE XI—Actinomyces granule surrounded by leucocytes. Note the basophilic central mass of mycelium and the radiating marginal acidophilic clubs.



probable that in man and animals it gains entrance through abrasions. Such abrasions may be induced by carious teeth or by accidental trauma. It is possible that minor abrasions may be produced by uncooked grains and cereals or by straws. The organisms have been found upon kernels of grain, and such kernels have been recovered from the abscess cavities. The resistance of the organisms makes it possible that they may remain living in the dried state for a long time. The organism flourishes best on moist grains, and the disease is more prevalent in rainy years or damp seasons. The disease is most common in Austria, Germany, Switzerland and certain parts of Russia, all damp regions and all occupied with cereal cultivation and cattle raising. Sanford found that it is widely distributed in the United States, especially in the upper Mississippi valley and the northwestern states.

Actinomycosis in Man.—The disease occurs in adult life and is four times more frequent in males than females. A history of chewing wheat, oat or barley spears is very common. The organisms enter through a minor abrasion, either with or without particles of grain. They attack the jaw, mouth, tongue, tonsil and ileocecal region and appendix. The lesion occurs sometimes in the skin, the breast, the liver, lung, brain and other parts of the body. Although essentially a local inflammatory process, it may spread extensively and metastasize; by virtue of secondary infection it may be febrile and may result in a bacterial septicemia or pyemia.

Grossly, it may be either a moderately or greatly swollen, red, tender mass, dense on the outer surface, often with a soft or semifluctuant center. Sometimes, however, there is little redness and the mass resembles a tumor. Single or multiple sinuses appear, from which is discharged a creamy yellow or brownish-yellow pus containing the characteristic granules, usually somewhat less than a millimeter in diameter. These can be pressed between slides, forming masses about 2 mm. in diameter, which show upon microscopic examination a network of branching threads and numerous club shaped bodies, the enlarged termini of the threads. In order to inoculate culture media successfully, the granules should be well washed and inoculated in large quantities upon a considerable number of media and incubated both aërobically and anaërobically. Secondary infection is so common that contamination is frequent. After primary growth is obtained, secondary culture is usually successful. In pulmonary lesions the granules may be found in the sputum. Examination of the pus shows a considerable content of fat and lipoids, which often suggests the diagnosis.

Microscopic examination of tissues has shown that the lesion begins as an accumulation of polymorphonuclear leucocytes about the organism, followed by a massing of endothelial cells and then a layer of granulation tissue and fibrosis. Giant cells are occasionally encountered. The lesion enlarges by progressive extension of the process accompanied by destruction of the invaded tissue, and necrosis of the central parts with abscess formation. As the disease advances, the abscesses rupture on surfaces and chronic sinuses result; the lesion is highly invasive and appears to break down bone as readily as soft

tissues. Blood vessels become the seat of thrombosis and may be invaded so that organisms can be transmitted to neighboring organs. As in the pus, so in the tissue sections, fat and lipoids can be demonstrated in a few of the leucocytes and in many of the endothelial cells. The diagnostic feature is the presence of the organism in the typical granules. In tissue sections, with the ordinary stains, the central mass of organisms takes the basic stain and may be distinctly granular as the result of degeneration. Around this is a band of radiating threads terminating in club like extremities. The core of each club is a thread of organism and takes the basic stain; the club, however, is a transformation product probably degenerate in character, and takes the acid stain. Only fine technique demonstrates the thread in the center of the club. Sometimes the clubs are not formed and the termini are bare. Wright's studies indicate that the formation of this acidophilic gram negative shell about the termini is probably a protective mechanism of the actinomyces against the resisting forces of the animal host.

The disease may produce death by invasion of organs or tissues necessary to life, or by secondary infection. Excision is usually successful, where practicable. Specific therapy with iodides is recommended, but since the surrounding fibrosis may naturally result in encapsulation and cure of the disease, there is some doubt as to the real value of iodide therapy.

MADURA FOOT

Madura foot or mycetoma is a disease of warm climates, first recognized and prevalent in India. It is due to the actinomyces *madurae*, an organism resembling that of actinomycosis, but strictly aërobic, a spore former and not pathogenic for lower animals. Clinically identical cases have been caused by other organisms such as actinomyces *bovis* and *aspergillus*. Lesions are especially likely to be found on the foot as dense swellings, which soon break down with the formation of sinuses and discharge of pus. The lesion rarely extends up the legs, is less invasive than actinomycosis, but may expose tendons and bones with little direct destruction. The pus is a sticky, viscid, yellow pus containing granules about the size of those in actinomycosis. The granules may be dense and dark brown or black, the "melanoid" granules, or soft, friable, grayish-white or yellow, the "ochroid" granules. The granules may be melanoid because of blood pigment or because of the presence of a special pigment producing variety of the organism (see Gammel et al.). Histologically, the granules are found to be made up of a central tangle of threads surrounded by radiating filaments with club shaped extremities. The lesion microscopically is much like that of actinomycosis, but the marginal fibrosis is usually much more prominent in madura foot and the connective tissue cells show many hyaline granules, Russell fuchsin bodies. About the masses of organisms are often found golden brown granules of iron-bearing blood pigment. Apparently the only satisfactory treatment is complete excision of the affected area.

Other actinomycetes producing abscesses include the actinomyces *Thi-biergi* which produces the so-called cutaneous discomycosis; the actinomyces *asteroides*, isolated from a brain abscess; and certain others of less importance.

STREPTOTHRICOSIS

Cases of disease of the lungs have been recorded, apparently caused by a branching filamentous organism, which cannot be definitely classified as actinomyces *bovis* or actinomyces *maduræ*. The organisms of streptothricosis probably represent a group rather than a single organism, since in different cases they vary as to staining properties and when cultivated (with difficulty) are sometimes aërobic and sometimes anaërobic. Claypole would include in the group of streptothrices acid-fast bacteria, such as bacillus tuberculosis and bacillus lepræ, bacillus diphtheriæ, the mycelium forming organisms and the higher sporulating fungi. The disease clinically may resemble tuberculosis, as in Flexner's case, gangrene as in Ophül's cases or pneumonia as in Lenhartz's case. The gross morbid anatomy may be that of tuberculosis, and the condition may be combined with tuberculosis. The lungs, however, are likely to show extensive consolidation with necrosis and multiple cavity formation. There may be either acute fibrinous pleurisy, empyema or chronic fibrous pleurisy. Microscopically, the lungs show a rich infiltration of leucocytes both in the alveoli and tissues of the lung, necrosis, and in some areas an infiltration of large mononuclear cells. In the more chronic cases, such as those described by Bridge, there may be extensive formation of granulation tissue, associated with small giant cells. Isolated lesions may resemble tubercles very closely. They show central necrosis, endothelial cells and giant cells, but in the layer of endothelial cells and surrounding lymphoid cells there is a definite formation of fibroblasts and new blood vessels. The organisms may be demonstrated in the tissues. The lesions are commonest in the lungs but may appear in lymph nodes, omentum and other viscera. The sputum may sometimes show granules like those of actinomycosis. They are usually gram positive and stain with carbolfuchsin; they may or may not be acid-fast. They can also be demonstrated in the pus of open lesions.

BLASTOMYCOSIS OR OIDIOMYCOSIS

Introduction.—Blastomycosis is a specific infectious granulomatous process, which manifests itself either as a skin disease or as more widely disseminated multiple abscesses of the deep organs and the skin.

It is due to microorganisms of the order of hyphomycetes. Gilchrist first described the skin lesions of the disease and with Stokes identified the cause as blastomycetes, naming the condition blastomycosis cutis. Busse and Buschke had previously described a pyemic condition with skin lesions, identified the cause as saccharomyces *hominis* Busse and called the condition saccharomycosis *hominis*. Hektoen, Brown, Davis and others have studied the organism, but much of our information is due to the work of H. T. Ricketts. Ricketts pointed out that the organism is an oidium. It multiplies in the tissues by budding of oval cells, but on culture media may grow: (1) as a smooth pasty mass without aerial hyphæ, proliferating chiefly by budding or by mycelial formation and segmentation; (2) with a granu-

lar surface without true aerial hyphæ, penetrating the substratum and proliferating by formation of segmented mycelium, with separation of the elements after the manner of oïdium; (3) as mould fungi with the growth possibilities of the first two, in addition formation of aerial hyphæ with lateral conidia and terminal ascospores or naked spore groups. Thus, it will be seen that the organisms from a large group of clinically and pathologically similar cases, may be culturally either blastomycetoid (yeast-like), oïdium-like, or hyphomycetoid. Wade and Bel apparently prefer to recognize two groups, including as one group groups 2 and 3 of Ricketts. Decolorized by the ordinary gram method, they may be positive with the Weigert modification. They take basic dyes somewhat more readily than acid dyes. In the tissues the organism appears in the form of oval bodies with homogeneous, doubly contoured capsule, beneath which a space separates the capsule from the finely or coarsely granular, sometimes vacuolated, non-nucleated, protoplasm. Budding is often seen and rarely small spore-like bodies are found. The organisms measure 10-20 micra but may be larger or smaller.

The mode of transmission is not clearly known, but such organisms occur free in nature and accidental trauma may provide a mode of access. Stober brings forward evidence to indicate that rotting wood may be a source of infection in certain cases.



Fig. 121—Photograph of late lesion in blastomycosis. Note central healing and marginal active lesions. Patient of Dr. H. N. Cole.

Morbid Anatomy.—The disease is far more common in males than in females, occurs most frequently in middle life but is seen at other periods. The skin lesion often follows a minor injury and appears first as a papule which becomes pustular, ulcerates, discharges tenacious pus and gradually extends. The surface of the larger ulcer is studded with soft nodules, and is surrounded by a red areola in which can be found many minute intracutaneous abscesses. As the lesion advances, healing is likely to occur in the older central part, and in the prolonged cases cicatricial contraction

may be marked. The hands, forearms, and head are most often attacked, although the disease occurs in other parts. The disease progresses slowly, usually over many months. Histologically, the ulcerated area shows absence of epithelium. Other parts show a thickened horny layer, and also extensive downgrowth of irregular processes of the interpapillary epithelium; the prickle cells are enlarged and show prominence of the cell bridges. The epiderm commonly shows a diffuse but scanty infiltration of polymorphonuclear leucocytes and lymphoid cells. Miliary abscesses are common in the epiderm at the margins of the lesion; these are made up principally of leucocytes, but other inflammatory cells appear and sometimes a few threads of fibrin are present. The corium, particularly in the upper layers, is infiltrated with leucocytes, lymphoid cells, endothelial cells, plasma cells, granular mast cells and giant cells. In the older cases, granulation tissue is likely to be found, partly or completely converted into scar tissue. Giant cells are found in epiderm

and corium, are of the foreign body type with large cytoplasm and irregularly distributed large vesicular nuclei. They usually contain one or more blastomyces. Ricketts was of the opinion that the giant cells originate from epithelial cells, but it is possible that those in the corium are of endothelial origin.

Systemic blastomycosis may involve any of the deep tissues of the body. Entrance is through the skin or the respiratory tract, rarely through the



Fig. 122—Blastomycosis cutis, showing interpapillary prolongations of the rete mucosum and at m. a milium abscess. From Hartzell, *Diseases of the Skin*.

intestinal canal. Entering through the respiratory tract the organisms lodge in the smaller bronchi or bronchioles and a bronchopneumonic patch is established, followed by growth of the organisms. The lesions resemble tubercles grossly, but microscopically may be either a collection of blastomyces with a small surrounding area of necrosis, a tubercle-like lesion with central necrosis, epithelioid and giant cells, or an abscess rich in polymorphonuclear leucocytes. In any of these, the lesion is identified by the presence of the organism. There is an associated chronic pleurisy. The lesion extends through the lymphatics and may produce marked lesions in the mediastinal nodes. Essentially the same lesions are found in the other viscera attacked.

Immunity.—Hektoen was able to produce agglutinins by successive inoculations of the organism. Davis found that the vaccinated guinea pig walls off infection more readily than the normal animal, and that immune serum reduces the growth activity of the organisms *in vitro*. Agglutinins were absent and low titre precipitins variable in the guinea pig immune sera. Lytic and complement fixing bodies were not demonstrable, nor were cutaneous and ophthalmic reactions obtainable. Anaphylactic manifestations were not definitely demonstrated. Phagocytosis by peritoneal cells is fairly active, but opsonins appear to have no great influence on the process. Cutaneous reactions have been tried in man but without clear cut results. Other immune reactions in man are not demonstrable. It may be said that natural and artificial infection with blastomyces lead to little or no immune reaction.

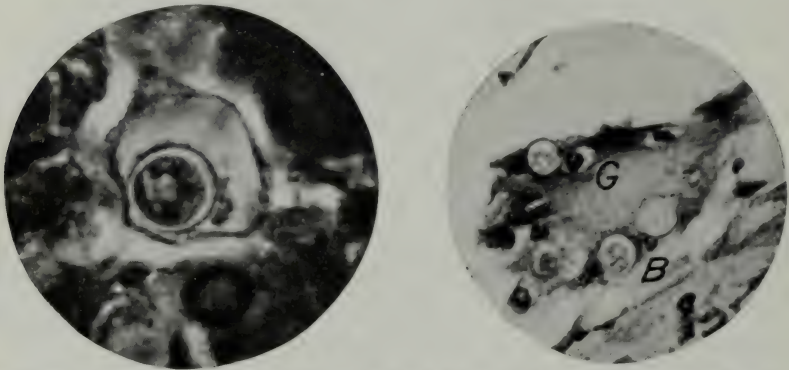


Fig. 123.—High power photomicrographs showing parasite in lesion, and a giant cell. From Hartzell, *Diseases of the Skin*.

Experimental animals are susceptible to inoculation, but as a rule natural healing results; only occasionally are widespread or fatal experimental lesions encountered except following intravenous inoculation.

The human cutaneous disease runs a chronic course with remissions and exacerbations. Under proper treatment cures are effected. The systemic disease is fatal after a less prolonged course.

COCCIDIOIDAL GRANULOMA

This is a disease, which in many respects resembles systemic blastomycosis, and there is little doubt that in certain instances the two diseases have been confused. The studies of Ophüls, Hektoen, MacNeal and Taylor, Wolbach, Brown and Cummins, have established the identity of coccidioidal granuloma. Most of the cases have been reported as originating in the San Joaquin valley of California, but cases of what appears to be the same disease have occurred in the Eastern United States and in Europe. The disease is usually systemic but cutaneous cases, notably that of Wolbach, are on record. Cutaneous manifestations are by no means so common as in blastomycosis. Clinically, the disease closely resembles tuberculosis and shows a greater disposition to lymph node involvement than is true of blastomycosis. The organism, cocci-

dioides immitis, is culturally and morphologically distinct from *blastomyces*. Pathologically, the gross lesions resemble tuberculosis and the microscopic picture is so closely similar, that it is distinguishable only by the presence of the organisms. In the tissues, the organisms appear as doubly contoured spheres, variable in size and measuring from five to fifty micra. Within the hyaline capsule is a granular protoplasm and not infrequently small spherules which are almost certainly endospores. These organisms differ from those of *blastomycosis* in that they multiply by endosporulation in the tissues and not by budding. Initial cultural growth is more rapid with *coccidioides* and proceeds best at 37° C. rather than 20° C., the optimum for *blastomyces*. Anaërobic cultivation shows multiplication by the formation of mycelium and chlamidospores at the termini of, or within the threads. Rabbits and guinea pigs are more susceptible to *coccidioides* than to *blastomyces*. The disease in man affects males much more often than females, clinically and pathologically resembles systemic tuberculosis, is more unusual as a cutaneous lesion than *blastomycosis*, and although always fatal is more favorably influenced by administration of iodides than *blastomycosis*.

TORULA INFECTIONS

Distinct from *blastomycosis* and *coccidioidal granuloma*, but apparently somewhat confused with these, are cases due to infection with the *torula histolytica* of Stoddard and Cutler. The infection may appear in the brain and meninges, lungs, liver, spleen and kidneys but does not affect skin or bones. The lesions grossly resemble tuberculosis and in the meninges may suggest syphilis. Microscopically, there is destruction of tissue, which may be visible grossly as a gelatinous mass. In connection with the necrotic area is an infiltrate of lymphoid and endothelial and plasma cells, often associated with some fibrin formation and practically always with multinuclear giant cells; polymorphonuclear leucocytes may appear but not in large numbers. The organisms appear free or within giant cells and endothelial cells. They are small spherules, one to thirteen micra in diameter, which stain well with ordinary basic dyes and in the larger forms show a refractile capsule. Proliferation in tissues is by budding. Upon inoculation it is highly pathogenic for mice and rats, slightly so for guinea pigs, rabbits and dogs, and has an especial affinity for the central nervous system. Culturally, it proliferates by budding and never produces mycelium.

SPOROTRICHOSIS

This disease was first described in this country by Shenk, further studied by Hektoen and Perkins and subsequently in Europe, particularly by de Beurmann and Gougerot. The disease is caused by *sporotrichium* which was formerly said to have three varieties, but the studies of Meyer and others would indicate that these varieties cannot be definitely separated by morphological, cultural or immunological examinations. The organism grows well on

solid and liquid media, particularly two to four per cent. dextrose agar. It is an obligate aërobe and does not produce gas. Examination of cultures shows a tangled branching septate mycelium, from the ends and sides of which small conidial spores appear. The disease may occur at any time of life and appears to be somewhat more prevalent among farmers than others, where the organism is inoculated from growth on vegetables. The primary lesion usually follows an injury, although this does not appear to be true in all cases. The incubation period is usually several weeks but may be as short as ten days. The primary lesion begins as a small, painless subcutaneous papule several millimeters in diameter, slightly reddened and sometimes slightly tender. Secondary lesions appear along the course of the draining lymphatic vessels. The lesions may remain as of somewhat gummy consistence without ulceration, but usually break down and discharge a viscid, white, yellow or brown pus. According to de Beurmann the forms to be recognized are, localized with neighboring lymphangitis and lymphadenitis; disseminated gummatous sporotrichosis with multiple subcutaneous nodules, distributed throughout the body without ulceration; disseminated ulcerative sporotrichosis with multiple ulcers over the body, resembling the ulcerative lesions of tuberculosis, syphilis or furunculosis; and extracutaneous sporotrichosis appearing in mucous membranes, muscles, bones, joints, eye, synovial membranes, kidney and lungs. Warfield's case is one of a few of widely disseminated sporotrichosis reported in this country, but cases with less extensive lesions are not uncommon (Guy and Jacob). In the commoner ulcerative forms the primary lesion breaks down and discharges pus, and this is followed after variable periods by secondary lesions along the lymphatics, which also break down. The ulcers show a red suppurating base and firm elevated margins. Histologically, the lesion may appear as an abscess with surrounding organization or, in the more prolonged forms, as a focal accumulation of polymorphonuclear leucocytes, endotheliocytes, and in the margins, fibroblasts, new formed blood vessels and plasma cells. Neither the pus nor the microscopic section of the lesion is likely to show the organism, except that occasionally fragments of more or less degenerate mycelium may be found within endothelial cells or giant cells. The diagnosis depends upon recovering the organism, which can frequently be obtained in pure culture. The mycelial cells are about two micra broad, about thirty to forty micra long and the spores about two by four micra. These spores show a dense hyaline capsule and occasionally a small vacuole in the cytoplasm. The cultures grow at 37° C. but apparently attain their best growth at about 20° C. Local lesions may be produced experimentally in animals but upon intraperitoneal injection into rats, lesions are produced in the testicle and cord from which pure cultures may be obtained, and which show the organisms in microscopic section. Using spore suspension as antigen the patient's serum may agglutinate in dilutions of from one to eighty to one to one-thousand. Using either spores or culture material as antigen, complement fixation tests with patients' sera are positive. Both intracutaneous and subcutaneous reactions with killed spores usually give definite positive reactions

The same disease occurs in the horse, dog, rat and certain other animals. In the horse it closely resembles epizootic lymphangitis but is distinguishable by cultural methods. Certain cases in man are due to infection from contamination by diseased animals.

ASPERGILLOSIS

Fungi of the genus *aspergillus* may be pathogenic for man, and no less than eleven species have been recognized in lesions of varying situation and severity. The commonest in nature and the commonest found in man is *aspergillus fumigatus* Fresenius. It is found in various cereals, straw, hay, etc. It produces a dark green or brown growth in culture and shows branching mycelium two to three micra in diameter. The hyphæ are wider, are surrounded by rounded bodies from which radiate sterigmata made up of a chain of conidia, 2.5 to 3 micra in diameter. Aspergillosis occurs in France among breeders of pigeons; both are probably infections by the grains used for feeding the birds. It is not uncommon in India and other tropical countries. Birds are susceptible naturally and experimentally, and the disease has been produced in monkeys. Mammals, such as the sheep, may be affected.

Aspergillus may lodge and grow in the respiratory tract without producing lesions or may lead to pseudomembranous or ulcerative lesions. Much more serious is the development in the lungs of pseudotuberculosis *aspergillina* or pneumokoniosis (preferably pneumomycosis) *aspergillini*. The lesions grossly resemble tuberculosis in miliary and conglomerate forms; they may be pneumonic in type and may also exhibit cavitation. Coarse granules may be found in the lesion, made up of organisms; if *fumigatus*, dark brown or green, if *aspergillus niger*, black in color. Microscopically, the earlier lesions show an infiltration of leucocytes, followed later by the presence of epithelioid and a few giant cells. The latter are of the foreign body type and may contain parts of the organism. Central necrosis begins early, but does not progress far because of the early fibrosis and marginal vascularization. The surrounding lung may show reactive pneumonia and extensive diffuse fibrosis. Cavitation occurs as the result of secondary infection. The early lesions may show mycelia and spores, but they are sparse and difficult to find in the later stages. The cultures develop toxic bodies which produce tetanic convulsions and paralysis in animals.

Aspergillosis of the lungs is likely to be associated with similar lesions in liver, kidney and other organs. Apparently organisms may enter through the intestine and infect the mesenteric lymph nodes. Lesions may be produced in superficial parts such as the eye, ear, nose, urethra, skin, and may infect wounds and ulcers.

Emerson has reported pulmonary lesions presumably due to *penicillium*, an organism closely related to *aspergillus*, and although he apparently rules out *aspergillus*, he does not identify the species of *penicillium*.

HODGKIN'S DISEASE

Introduction.—Hodgkin's disease exhibits a progressive enlargement of the lymph nodes, occurring in chains or groups rather than in individual nodes, extending over a period of months or years, accompanied by anemia and cachexia. The clinical features were described by Hodgkin in 1832. The disease was subsequently described in greater detail and differentiated as a clinical entity by Wilks in 1856, who gave it the name which it now bears. Numerous other terms have been applied including pseudoleucemia, lymphogranulomatosis and lymphogranuloma malignum. It was regarded as neoplastic for many years following its identification, and even in recent times



Fig. 124—Photograph of patient the victim of Hodgkin's disease involving cervical and axillary lymph nodes.

several authors have concluded that the disease should be regarded as a variety of malignant tumor. Nevertheless, the majority of opinion is definitely inclined toward the view that the lesion is of granulomatous character. In 1898 Sternberg published the first of a series of papers indicating that the disease is probably of tuberculous nature. This was followed in 1902 by the work of Reed which indicated beyond question that it is a clinical and pathological entity and, on both pathological and experimental grounds, not caused by the tubercle bacillus. This was further confirmed by Longcope in 1904, who described the histological picture in great detail. The histological differences between diffuse tuberculosis of the lymph nodes and Hodgkin's disease were pointed out by Karsner in 1908. The lesions are usually well confined by the capsule of the involved nodes or spleen and practically never appear in situations where there is not preëxisting lymphoid tissue. Invasion, therefore, is slight if present at all, and there is little indication that metastasis occurs.

The cause of the condition is not as yet definitely known, although numerous interesting studies have been conducted in relation to its etiology. In 1902 Fränkel and Much reported finding in the lymph nodes of Hodgkin's disease a gram positive somewhat granular bacillus which they regarded as a non-acid-fast tubercle bacillus. In 1907 White and Proescher described in the nodes a spirochete, but this finding has not been widely confirmed and the organism is not now considered as a probable cause of the disease. In 1913 Negri and Mieremet, and Bunting and Yates independently isolated from cases of Hodgkin's disease a diphtheroid bacillus. This grows readily on ordinary media at 37° C. and in culture is likely to be pleomorphic including the bacillary forms, club-shaped, so-called involution forms, coccoid, and branching forms. Grown in pure culture and inoculated subcutaneously into monkeys, it is claimed by Bunting and Yates that lesions very closely resembling Hodgkin's disease appear in the lymphoid apparatus in the monkey, and that there is an associated change in the blood picture similar to that occurring in human Hodgkin's disease. The organism has been obtained from Hodgkin's disease by other observers and has also been recovered from lymphosarcoma, arthritis deformans, hyperplastic tuberculosis, leukemia and leprosy. It is known to occur free in nature. Bunting is of the opinion that the various

pathological manifestations may be due to some variation in the organism, or to variable conditions in the host, whereby differences in reaction are determined. Although in the hands of Bunting and Yates vaccine treatment appeared to be successful, nevertheless, this is not a common experience. It must be admitted that the organism is commonly present in Hodgkin's disease, yet it would appear that more work must be done before it can be stated finally and positively that this diphtheroid is the cause of the disease.

Clinical Manifestations.—Although conditions closely resembling Hodgkin's disease occur in swine, horse, chicken, dog and sheep, nevertheless, it

exhibits its most characteristic changes in man. According to the studies of Ziegler, the disease is most common between twenty and thirty-five years of age and is distinctly more frequent in males than in females. The youngest recorded case is a child of five and one-half months and the oldest a patient of seventy-six years. The primary change affects more commonly the right cervical chains, as a slowly progressing painless enlargement. Numerous cases are on record, however, in which the primary lesion is elsewhere and in which the cervical lymph nodes are not affected. It may be primary in the spleen, in the gastrointestinal canal, the mediastinal or retroperitoneal lymph nodes or other situations in which lymphoid tissue is to be found. The enlargement may progress gradually, or may be augmented at certain periods in association with febrile attacks. As months go on, the spleen is likely to become involved and a widespread lymphoid enlargement may be observed. The progress of the disease may be accompanied by loss of flesh and strength, although decreases in weight are not likely to be very marked. The blood often shows a slight degree of simple anemia. In the earlier cases, particularly during the first year of the disease, the leucocytes in the circulating blood may be normal in number or slightly increased in number. Subsequently, they may be very considerably increased in number without any evidence of suppuration in any part of the body. Differential examina-



Fig. 125—Hodgkin's disease involving cervical and upper mediastinal lymph nodes.

tions in which lymphoid tissue is to be found. The enlargement may progress gradually, or may be augmented at certain periods in association with febrile attacks. As months go on, the spleen is likely to become involved and a widespread lymphoid enlargement may be observed. The progress of the disease may be accompanied by loss of flesh and strength, although decreases in weight are not likely to be very marked. The blood often shows a slight degree of simple anemia. In the earlier cases, particularly during the first year of the disease, the leucocytes in the circulating blood may be normal in number or slightly increased in number. Subsequently, they may be very considerably increased in number without any evidence of suppuration in any part of the body. Differential examina-

tion of the blood shows that in those instances where the total white count is normal, the polymorphonuclear leucocytes are not increased, or are slightly decreased. In these cases the so-called large transitional cells are distinctly increased in absolute and relative number. In the cases with leucocytosis, the polymorphonuclears are proportionately increased, and the large transitionals show an absolute and sometimes a relative increase. The lymphocytes are not likely to show any change except for very slight increase during the earlier months of the disease, followed by a gradual diminution until finally they are present in smaller proportion than normal. The eosinophiles are variable, in some cases being distinctly increased and in other cases normal or less than normal. Examination of the blood platelets shows a distinct increase, and megalokaryocytes may be found. Histologic sections show megalokaryocytes in capillaries in many tissues. The disease progresses to a fatal termination, sometimes occupying six or eight months and sometimes several years.

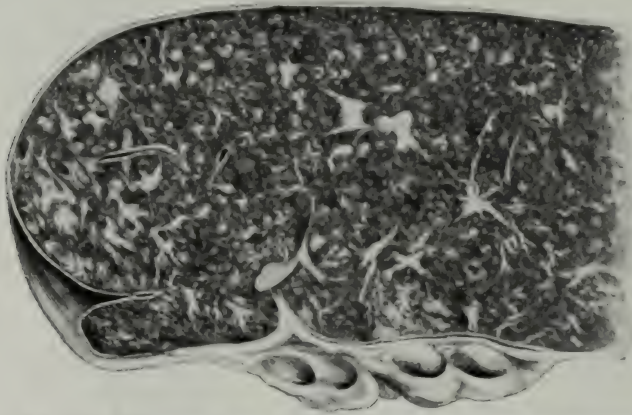


FIG. 126—Cut surface of spleen in Hodgkin's disease, showing extensive fibrosis and small areas of necrosis.

Morbid Anatomy.—The lymph nodes are found to be enlarged in chains or groups. They are pale in color and of increasingly dense consistence as the disease is of greater duration. There is usually a chronic inflammatory change in the tissues surrounding the individual nodes, so that they are adherent to one another. Cross section of the nodes shows that they are discrete and there is little tendency for invasion of the capsule or fusion of the lymphadenoid tissue. The cut surface is moist, pale, in the earlier stages bulges, and in the later stages does not. It is firm in the later stages, and in any stage may show small areas of yellow or yellowish-gray necrosis. Microscopically, the picture differs according to the stage. The earliest changes noted are proliferation and hyperplasia of the lymphoid cells with partial or complete obliteration of the architecture. In the germinal centers of remaining follicles and in situations which can safely be estimated as the original position of follicles, hyperplasia of germinal centers can be found. The sinuses show extensive endothelial hyperplasia. It cannot definitely be stated whether this hyperplasia is from the lining endothelium, or is also participated in by the cells of the reticulum.

As time goes on, the architecture of the node is definitely obliterated and the cell picture is characteristic. There is hyperplasia of the lymphoid cells and an associated increase in endothelial cells, numerous plasma cells, an occasional mast cell and varying numbers of large mononuclear and multinuclear giant cells. The giant cells are several times the diameter of the endothelial cells and show a generally homogeneous cytoplasm. The nuclei are large and distinctly vesicular and in the multinuclear forms override one another. Eosinophiles are frequent in many cases but absent in a considerable number of others. An important feature of the histology is the proliferation of the connective tissue. In the earlier stages this is slight but as the disease progresses, fibrosis may form a very prominent part of the picture. Longcope divided the disease into three stages on the basis of the degree of fibrosis, but it can readily be seen that such a division is purely arbitrary. Nevertheless, it is possible to distinguish early and late cases on this basis. Necrosis appears in the form of small areas with loss of cell outline, pyknosis, karyolysis and karyorrhexis; it affects the cellular rather than the fibrous parts. Granules of golden brown pigment are often present but their nature is not definitely known.



Fig. 127—Histology of lymph node of Hodgkin's disease, showing extensive fibrosis and several types of cells.

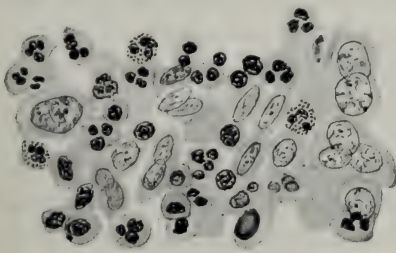


Fig. 128—Cell detail in Hodgkin's disease. Note the various forms of giant cells, endothelial cells, a plasma cell, polymorphonuclear leucocyte, and several granular eosinophiles.

Of the other organs of the body, the spleen is frequently and in fact almost constantly involved. This organ is large, firm, dense, shows a thick slaty capsule and in cross section is firm, red, and may show areas of necrosis. Connective tissue is obviously increased but the follicles may or may not be visible. The histology of the spleen is essentially the same as that of the lymph node, although in this situation pigmentation may be more prominent. The liver is usually somewhat enlarged, but shows no particular gross characters. Microscopically, however, there are sometimes found in the peribulbar connective tissue, cell masses similar to those in the lymph nodes. These, however, are not encapsulated and may appear to invade the liver tissue.

The bone marrow is usually normal in appearance grossly, although microscopically hyperplasia of various elements may be observed. This, however,

usually depends upon the degree of associated anemia and does not appear to be an essential part of Hodgkin's disease.

The functional disturbances incident to the disease are very largely the result of local compression, anemia, and cachexia. The importance of pressure depends entirely upon the situation of the enlarged nodes. Sometimes compression of important nerves in the neck or vascular trunks in various situation occurs, and if the mass happens to be in the central nervous system, as for example in the spinal canal, motor and sensory disturbances may occur.

MYCOSIS FUNGOIDES

Mycosis fungoides or granuloma fungoides is a chronic and almost invariably fatal granulomatous condition of the skin, of unknown cause. It was originally thought to be a variety of sarcoma but is now considered inflammatory. Although many dermatologists regard it as a cutaneous manifestation of Hodgkin's disease, there are minor differences in the character of the lesion; these, however, may be due to its situation in the skin. Its maximum frequency is between forty and sixty years of age, somewhat later than Hodgkin's disease, and it is about equally distributed between males and females (Hartzell). Clinically there are three stages: the first, a dermatitis usually of eczematoid type; the second, an infiltrative stage in which papules appear; and the third, a stage of formation of cutaneous nodules from a few millimeters to several centimeters in diameter. The first stage may last many months or years, the second is of shorter duration and in the third stage the patient is likely to exhibit general symptoms. The nodular lesions tend to break down and ulcerate. These may heal and other newer lesions follow the same course.

Histologically, in the lesions of the early stage, the premycotic stage, there is thickening of the epidermis, prolongation of the interpapillary portion, and an infiltration into the corium, especially the papillæ, of lymphoid cells with a few plasma and new connective tissue cells. The nodules are made up of lymphocytes, plasma cells, endothelial cells, leucocytes, eosinophiles, mast cells, multinucleated giant cells and connective tissue cells. These are irregularly intermingled much as in Hodgkin's disease. Karyorrhexis is common and mitotic figures in cells closely in relation to the small areas of necrosis are not infrequent. The giant cells show vesicular over-riding nuclei; the nuclei are somewhat more numerous than is usual in the similar cells of Hodgkin's disease. The connective tissue may not increase until late in the disease. The blood vessels are dilated and in late stages may show hyaline degeneration of the walls and thrombosis, the latter leading to edema of the tissues. Various bacteria are commonly present as the result of secondary infection. A general anemia may accompany the disease, sometimes associated with a relative increase of the circulating eosinophiles.

GRANULOMA INGUINALE

This is a chronic granulating ulceration of the inguinal region or perineum which may also involve the external genitalia, surface of lower abdomen, inner

surface of thigh, anus and vagina. It is endemic in tropical and subtropical countries and has been called granuloma venereum and granuloma pudendi ulcerativum. Within the past few years numerous cases have been found in temperate countries, most commonly in large general hospitals and almshouses. It occurs in negroes more frequently than whites and attacks both sexes. It has been variously ascribed to syphilis and tuberculosis, but although syphilis is not infrequently associated, it is now considered a clinical and pathological entity. Various spirochetes have been found in the lesion but these are only superficial and probably secondary invaders. In the deeper parts of the lesion, particularly in the active and progressing cases, are found small bodies, first described by Donovan, within macrophages and free. Morphologically, these are coccoid, diplococcoid or short bacillary forms enclosed in what appears to be capsule. Walker has grown these in pure culture and considers that they belong in the group of *bacillus mucosus capsulatus* of Friedländer, although Aragao and Vianna believe the organism constitutes a new and separate genus.

The lesion may be preceded by venereal disease or trauma of the external genital organs, but is not in itself necessarily of venereal origin. It begins as a small papule, usually painless, which soon breaks down with the discharge of a thin serous material. The ulcer so formed gradually extends and after several months may cover a large area. It is well defined, with an irregular, slightly elevated base, and a sluggish red granular surface on which is a thin serous fluid sometimes condensed to form crusts. Smears from the deeper parts show the organisms described above. Histologically, there is usually an irregular downgrowth of the interpapillary epiderm, with loss of the surface epithelium and in places epithelial atrophy. Between the epithelial cords are found many lymphoid and plasma cells, endothelial cells and eosinophiles. Smears from the lesion show endothelial phagocytes which contain the organisms but they are difficult to find in sections. Phagocytosis of leucocytes, erythrocytes and cell fragments is common. Vascularization is not rich.

Treatment by intravenous injections of tartar emetic has been highly successful, although Lynch is of the opinion that if syphilis be associated, the antimony treatment should be supplemented with antiluetic therapy.



Fig. 129—Extensive ulceration of the perineum in granuloma inguinale.

Tropical ulcer or *ulcus tropicum* is a different condition attacking the legs and feet and due in large part to trauma. According to Wolbach and Todd the lesion is not to be regarded as a granuloma and is due in all probability to the *spirocheta schaudinni* (see also Corpus).

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CHAPTER XI

PROGRESSIVE TISSUE CHANGES

INTRODUCTION.

METAPLASIA.

HYPERPLASIA.

HYPERTROPHY.

FUNCTIONAL ADAPTATION.

TRANSPLANTATION.

PARABIOSIS.

EXPLANTATION (TISSUE CULTURE).

Introduction.—With the exception of the discussion of inflammation, much of the material of the preceding chapters has been concerned with regressive and destructive processes in the cells and tissues. In the chapter on inflammation the capacity of the organism to repair defects, either by regeneration of completely or partly destroyed tissue, or by organization and cicatrization, has been discussed. It must not be concluded that regeneration can be induced only through the medium of inflammation, for in lower forms, the injury necessitating regeneration may not be accompanied by inflammation, but in the higher mammals there are only rare instances in which the primary injury is not accompanied by some sort of reactive process exhibiting some or many of the phenomena of inflammation. It is for this reason that regeneration, organization, cicatrization and wound healing have been included in the chapter on inflammation. In addition, however, there remain certain other cell and tissue changes which, although they may be detrimental to the organism as a whole, are nevertheless, in so far as concerns cell or tissue, not regressive and tending toward death of the cell, but rather progressive in the form of multiplication of, or enlargement of cells. Associated increase of functional capacity may or may not occur, depending on the nature of the process. The complete discussion of these phenomena goes far afield in general biology and only the briefest presentation can be attempted here.

The general problems of this topic are concerned with cell division and growth. The discovery of karyokinesis has led to the intimate study of the process, and whilst it is undoubtedly of the utmost importance in the multiplication of the fertilized ovum and the development of embryo and fetus, there is some question that it plays a large part in maintenance of the cell constitution of adult tissues and there are those who maintain that amitotic cell division is, in the adult, of more importance. It must be admitted, however, that the replacement of cells destroyed in the normal wear and tear of the body of higher animal forms, is not available for wholly satisfactory examination, since the process is slow and material not easily secured for study save by fortunate circumstance. Tissues for this purpose cannot be obtained with the same control over time and place as is true of lower forms. The replacement of intestinal epithelium is frequently by mitotic division, but in normal skin where replacement is constant, evidences of cell multiplication are rare. Where replacement

is rapid, as in organizing tissues, mitotic figures are common. In regeneration of liver cells, amitotic division is much more common than mitotic division. It would appear then that both forms of cell division play a part in the progressive tissue changes of higher animals, but that the predominance of the one over the other varies with the location and conditions of the process.

The growth of cells is dependent upon nutrition and function. The maintenance of size of a cell depends upon a modicum of function in the presence of adequate nutrition. We have seen, in the study of atrophy, that if function be depressed over a sufficient length of time, atrophy will occur even though nutrition be adequate. As will be shown subsequently, increased activity, provided sufficient nutrition be available, may lead to enlargement or hypertrophy of the cell. On the other hand, demand for increased function associated either with an insufficient amount of nutrition or reduced capacity of the cell for assimilation, will lead to atrophy or degeneration and even to cell death. Thus functional demands have much to do with the size of a cell, but there is a necessarily close interdependence between function and nutrition. A disturbance of this relation may probably also lead to cell division, since the absorbing capacity of the cell is a mathematical function of its surface. As the cell enlarges, its surface is relatively reduced, and can only be restored by division of the cell.

There has been much discussion as to whether the stimulus to cell growth and division originates entirely within or outside the cell, but it must now be accepted that either or both may exist. The fertilization of the ovum gives an intracellular stimulus to cell multiplication. Nevertheless, the well-known studies of Jacques Loeb on artificial parthenogenesis show that changes in osmotic tension of the surrounding medium may induce cell division. This is primarily an external stimulus, regardless of whether its more immediate action is due to surface tension changes or to physicochemical changes in the intracellular protoplasm. Other factors influencing growth include temperature, which may be inhibitory, optimum, or stimulating, and chemical poisons, such as those of certain infectious diseases, which may lead to multiplication particularly of endothelial cells. Another phase, which will be referred to in the discussion of tumors, is the balance between the cellular constituents of tissues. It is maintained that the normal adult constitution of tissues is due to a mutual restraint exercised by the cellular elements upon one another so that none grows to excess. Weigert laid down the proposition that only when this restraint is removed can pathological growth ensue. Certainly disturbance of this balance, if it actually exist, is extant when one group of cells outgrows other cells, but that removal of restraint is the primary event is not finally established. Growth and multiplication may be induced by alterations of the relations of nutrition and function, by increased demand for function in the presence of adequate nutrition and capacity for assimilation, by thermal and chemical changes, by the process of fertilization, and perhaps also as the result of nervous influences. There is now no doubt that the glands of internal secretion have an important influence, not only on development but also on

growth. Development of sex characters is influenced by sex glands. Adult forms may also be altered by disturbances of endocrine glands, the most striking instance being in gigantism and the curious local overgrowth of extremities and lower part of the face, known as akromegaly, associated with lesions of the hypophysis. With all these facts in mind it must be concluded that cell multiplication and growth may be determined by intra- or extracellular factors. In multicellular organisms, especially the higher forms, blood and lymph supply, nerve influences, function and other forces and conditions are important in establishing and maintaining growth.

Metaplasia.—This term indicates the transformation of one type of cell into another and sometimes includes, with the morphological change, related functional alterations. Although not strictly a growth of cells, it is generally related to the group of conditions and processes discussed in this chapter. Before discussing the theoretical explanation of the process some examples are presented.

Epithelial metaplasia is seen in places where the surfaces are exposed to unusual conditions. The columnar epithelium of the gall bladder may become stratified squamous in type as the result of concrements in the bladder or of chronic catarrhal inflammation. Chronic catarrhs may induce the same change in that part of the larynx normally covered by cylindrical epithelium. Prolapse of the uterus, in which the organ drops into the vagina and eventually may protude through the vulva, leads to eversion of the organ so that the epithelium of the cervix and even of the fundus is exposed. If the condition persist for a sufficient time, the columnar epithelium becomes stratified squamous. In exstrophy of the urinary bladder the reverse process occurs, namely, a transformation of transitional into columnar epithelium, sometimes with goblet cell and crypt formation. Less common are similar changes in other situations, as for example metaplasia of bronchial epithelium into stratified squamous epithelium due to inflammation, and of duct epithelium of the pancreas into stratified squamous due to calculi, as reported by Haythorn.

Connective tissue metaplasia is strikingly illustrated in heteroplastic bone formation which was discussed in the chapter on calcification. This may be a direct transformation or occur through the intermediation of cartilage. It may follow a preceding calcification or appear as primary ossification, but in either case is usually associated with some type of inflammation.

In these examples the metaplasia is from one type of cell to another type representing the same embryonal layer. In other words, the law of tissue specificity is followed. This rule of metaplasia from one type of epithelium to another and of one type of connective tissue to another is general, and the process limited to these two types of tissue. Nevertheless, Krompecher has found in the study of tumors that epithelium may, through metaplasia, give rise to certain forms of connective tissue. That such metaplasia occurs in non-tumorous tissues has not been clearly demonstrated.

Most of the examples given illustrate the fact that metaplasia occurs in connection with inflammation. That the latter is the primary cause is not

always true, since in many instances the metaplasia appears to be the outcome of regeneration of certain elements. The place that regeneration occupies is indicated by the studies of Ribbert and of Carraro, who found that regeneration of salivary glands following partial extirpation is accompanied by epithelial metaplasia. Similarly Fütterer found the production of stratified squamous epithelium in the stomach of the rabbit following excision of a piece of mucosa, the metaplasia in this instance being in large part due to regeneration not complicated by inflammation. As has been indicated, tumor growth may be accompanied by metaplasia. The connection between these presumptive causes and metaplasia is not fully explained but the important hypotheses follow.

Virchow thought that metaplasia is a direct transformation of one type of differentiated cell into another and it seems probable that in a few instances such direct metaplasia occurs. Many of the more recent investigators consider that indirect metaplasia is much more common. This conception supposes that as a result of inflammation, regeneration, or tumor growth, the newly forming cells undergo a dedifferentiation or reversionary process in the direction of the primary embryonal or blastomere cell, and as further growth goes on there is a redifferentiation to form a type of cell not identical with the original type. This new differentiation produces cells of a lower order of specialization than the original, but may occasionally progress higher, the progressive or prosoplastic metaplasia. The reverse is called regressive or anaplastic metaplasia. Anaplasia will be discussed in the chapter on tumors.

It is possible that what appears to be metaplasia may be due to inclusion of embryonal remnants in the areas affected, which remnants may proliferate to form the new type of cells. This explanation does not, however, clarify the occurrence of stratified squamous epithelium in inflamed bronchi or ureter, and cannot be accepted as wholly inclusive. Such aberrations occur, but are not now regarded as metaplasia. False metaplasia is a change in cell form, accommodative in nature, exemplified by the flattening of lining epithelium in cysts, the production of spindle cell forms of epithelium in certain tumors and in epithelioid forms of connective tissue cells in chronic inflammations. Individual instances require careful examination to determine whether they are true metaplasias, aberrations or false metaplasias.

The studies of Wolbach and Howe indicate that avitaminosis, particularly vitamin A deficiency, may be the direct or indirect cause of "substitution of stratified keratinizing epithelium for normal epithelium in various parts of the respiratory tract, alimentary tract, eyes, paraocular glands and the genito-urinary tract," evidently a true metaplasia, and not of inflammatory origin.

Finally it must be kept clear that embryonal differentiation of cells whereby form changes and function appears, is differentiation and development, and not metaplasia.

Hyperplasia.—This is a truly progressive change in that it represents an increase in the number of cells in a part, usually as the result of inflammation

or irritation. As ordinarily applied, it does not necessarily indicate an increase in functional capacity of the individual cells, although frequently the increased number may augment function. In this respect it is difficult to differentiate hyperplasia from hypertrophy. Examples of hyperplasia are numerous. The multiplication of connective tissue cells in organization is hyperplastic. Local infection may give rise to enlargement of the lymph nodes draining the area, and on microscopic examination this is found to be due largely to an increase in the number of cells, particularly endothelial and to a lesser extent lymphoid. General infections may produce somewhat similar changes in lymphadenoid tissue throughout the body. Typhoid fever produces such changes in the lymphadenoid tissue of the abdominal cavity, lymph nodes, spleen and lymphoid follicles of the intestine; in this disease the hyperplasia affects especially the endothelial cells. Regeneration is essentially of the same nature but becomes truly hyperplastic when it exceeds the demands for replacement. Chronic catarrhs may lead to epithelial and connective tissue hyperplasia, forming polypoid growths; irritation of skin, as for example the lip by a pipe, may result in hyperplasia of the horny layers of the skin, i.e., hyperkeratosis. Deposit of dust in the lungs leads to an inflammatory hyperplasia of connective tissue. Numerous other examples might be offered.

The stimuli to cell proliferation may include all those factors discussed in the introduction to this chapter. It seems probable that bacterial products may play a part in the hyperplasias associated with inflammation and local and general infections. The experiments of Carrel indicate that substances extracted from leucocytes promote cell proliferation *in vitro*, and it is probable that hyperplasias in connection with acute inflammation may be similarly stimulated.

For clarification it should be stated that the term aplasia indicates failure of development of an organ or part from its embryonal anlage, and the term hypoplasia indicates that development is partial and incomplete. Regression from full development is indicated by the term atrophy.

Hypertrophy.—Hypertrophy is an increase in the size of a part or organ associated with an increase in functional capacity. Practically, the sole cause of hypertrophy is demand for increased function, although it is possible that nervous or hormonal or similar factors may operate in certain cases. Hypertrophy cannot occur unless there be an adequate supply of nutrition and the



FIG. 130—Acute hyperplasia of lymphoid follicles of intestine in typhoid fever.

cells can assimilate the nutritional elements offered. Hypertrophy of an organ may be due to an increase in size of its component cells, a simple hypertrophy. It is said that it may be due to an increase in the number of cells, a numerical hypertrophy, but no sharp line can be drawn between numerical hypertrophy and hyperplasia. The pregnant uterus is enlarged by hypertrophy of muscle cells and also by an increase in their number. Functionally, there is increased power of contraction. Similar confusion is found in other organs such as the thyroid. The physiological hypertrophy of skeletal muscle due to exercise is simple in type. Hypertrophies are also classified as to underlying causes. In addition to the physiological hypertrophies, examples of which have just been given, hypertrophy may be adaptive, compensatory, vicarious and perhaps irritative.

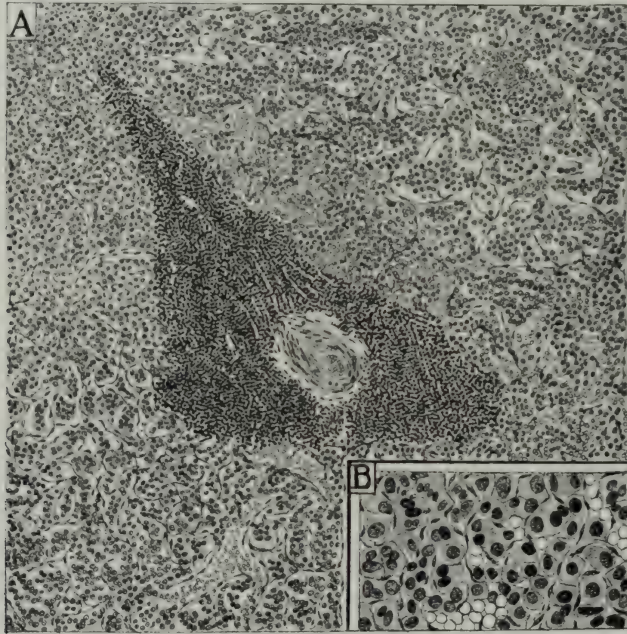


Fig 131—Endothelial hyperplasia in spleen. A. Low power. B. High power of cells of pulp.

Adaptation to a need for increased work is commonly illustrated in the heart, where lesions of valves, of pericardium, increased resistance to peripheral circulation, increase the work required. The muscular wall enlarges as the result of increase in the size of the constituent syncytial elements. Other hollow organs may undergo hypertrophy in order to adapt their musculature to the demands for work. Stricture of the urethra or enlargement of the prostate result in hypertrophy of the bladder musculature; pyloric obstruction induces hypertrophy of gastric musculature, and stricture of the gut, hypertrophy of muscle above. In all these instances, increased functional capacity goes hand in hand with the morphological change, but in the heart it is likely that dynamic reserve power is not increased and is probably not only proportionately, but also absolutely reduced.

Compensatory hypertrophy refers to that which develops as the result of loss or absence of a similar tissue. This is particularly well shown in paired organs. Congenital absence of a kidney or testis results in the opposite organ growing to about twice its normal size. If removed by disease or surgical intervention in early life the same result may be observed, but in later life such hypertrophy is not likely to occur. The same applies to removal of part of an organ, as liver or thyroid; the remainder undergoes hypertrophy to compensate for the deficiency. This is truly a hypertrophy only in reference to those portions remaining in the body, and does not exceed the bulk of the normal organs. In one sense, then, it is to be regarded as regeneration rather than hypertrophy.

The conception of vicarious hypertrophy is in certain instances not securely

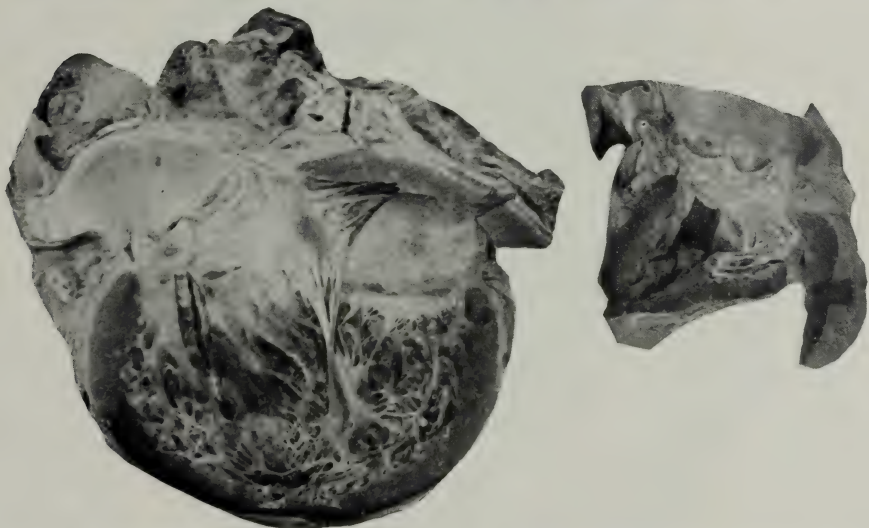


Fig. 132—Photograph of enormously hypertrophic and widely dilated heart in contrast to one of about normal size.

based on uncontroverted evidence, and the distinction between hypertrophy and hyperplasia cannot be sharply drawn. It is said that removal of the thyroid may result in vicarious hypertrophy of the hypophysis, that atrophy of the pancreas may be followed by enlargement of Brunner's glands. Similar inter-relationship between thyroid and adrenal as claimed by McCarrison is not clearly proven. Pearce and his coworkers, including the author, have pointed out that removal of the spleen leads to increase in size of lymph nodes with the assumption of the capacity for blood destruction. How these organs are stimulated to overgrowth is probably involved in the mysteries of the endocrine organs.

Chemical stimulation of growth has been demonstrated in the growth of bone due to minute doses of phosphorus, and of liver and kidneys by minute doses of arsenic and phosphorus. It is a far cry from this to the idea that bacterial products may lead to hypertrophy. Certainly they may produce fibrous hyperplasia, but it is probable that this is in part a replacement fibrosis

and even though it may be irritative in origin it is by no means a hypertrophy with increased function of the part. Chemical influences, not necessarily irritative, may be seen in hormonal stimulation to hypertrophy, the most notable example being the enlargement of the breasts in pregnancy. That this is hormonal rather than nervous is indicated by the experiments of Lane-Claypon and Starling who produced hypertrophy of the breasts and milk secretion, in non-pregnant virgin rabbits, by injecting embryo extracts.

Etymologically hypertrophy means over nutrition. No satisfactory evidence has been offered to show that an increased blood or lymph supply to a



FIG. 133—Hypertrophy of wall of bladder as result of obstruction by enlarged prostate. Note the heavy muscular trabeculae.

part can lead to hypertrophy. Excess of food supply to an individual may lead to obesity, a general deposit of fat in the fat depots, but there is no hypertrophy of an organ or part as the result; the fat deposit is usually a physiological process and the only pathological term that can be applied is infiltration.

Pseudohypertrophy is best illustrated by pseudohypertrophic muscular atrophy. Grossly, the muscles seem to be enlarged, but upon microscopic examination it is found that the muscle fibers are the seat of atrophy, and between them is such a rich infiltration of fat as to increase the gross size of the muscle.

Functional Adaptation.—Practically all the hypertrophies and certain of the metaplasias and hyperplasias serve to adapt the part involved to new func-

tional demands and altered conditions. There remain, however, certain evidences of functional adaptation difficult to include in these categories. These are usually in response to tension or pressure on a part. Probably the most striking examples are in bones. The arrangement of bony trabeculae, especially in the ends of long bones, and in the spongy bones, is such as to provide maximal strength. Acquired deformities, such as ankylosis, scoliosis, union of fractures in poor position, lead to differences in mechanical stresses upon the bone, which are ultimately met by a rearrangement of the internal trabeculae so as to meet better the new conditions. The transplantation of bone segments results in new bone, adapted in form to meet the mechanical strains and stresses of the part. Transplanted tendons show alterations in form and proportions of elastic and connective tissue fibers adapted to the needs of the new position. Occasionally, the endocardium in the ventricles immediately below insufficient semilunar valves, is thrown into valve-like folds which inhibit to some extent the regurgitation of blood. The mechanisms by which these changes take place are not understood, but it can be seen easily that they do not necessarily involve progressive changes such as hyperplasia or hypertrophy and are in no sense metaplasias. Jores has suggested the name *metallaxy*, but this is no more expressive of the condition than is functional adaptation.

Transplantation.—Marchand defines transplantation as the healing of a living part within or upon a different individual or another part of the same individual. This excludes the *implantation* of dead and inert materials, such as ivory, gutta percha, celluloid, etc., sometimes used to aid the surgical repair of defects of various kinds. Goldzieher and Makai emphasize the danger of confusion of these terms. The success of transplantation depends upon a variety of factors many of which are unknown. Autoplastic transplantation, the grafting of one tissue into the same individual, is more likely to be successful than isoplastic or homeoplastic transplantation, the grafting of tissue of one individual into another of the same species. Heteroplastic transplantation, the grafting of tissue into another species, rarely meets with success. The moving of an attached part to another part, the attachment remaining until healing has occurred, sometimes called attached or pedunculated transplantation, is a form of autoplastic transplantation, often successful but not strictly included in the usual meaning of transplantation. The index of success of transplantation is the permanency of life in the transplant, for many grafts live for a few weeks only to die and disappear.

Numerous factors governing transplantation have been studied, such as genetic relationship of donor and recipient or host, age, chemical factors of various kinds, blood supply, nerve supply, functional need of the transplant and others. As has been indicated, autografts are most likely to be successful, homeografts less so and heterografts rarely. Successful transplanting of skin, blood, bone and ductless glands is of the utmost practical importance and may be extended to include the transplantation of organs and limbs. Autografting is necessarily restricted in scope, and is practically limited to the transplantation of skin and bone, and to a lesser extent of ductless glands, most notably

the ovary. Homeografting may be understood to include also the transplanting or transfusion of blood. Heterografting if it could be placed upon a satisfactory basis would throw open a large field for transplantation of various tissues and organs which cannot be removed from human donors without great sacrifice or until death has occurred. Experimentally, transplantation is some-



FIG. 134—Microphotograph of connective tissue culture. From Carrel and Burrows, *Jour. Exper. Med.*

what more widely applicable than in human medicine, as for example, in the marvelous results obtained by Carrel in the transplantation of kidneys and limbs in animals, which depends upon careful maintenance of circulation by accurate suture of blood vessels.

The age and phylogenetic development of the subjects is of importance. In protozoan and lower animal forms success is greater than in the more highly differentiated species. Transplantations in embryo and fetus are likely to be more successful than in adults. The studies of Marine and others indicate that

youth is more favorable than later life. In vegetable life, transplantation is highly successful under proper conditions.

The tissue to be transplanted must be viable and the conditions to which it is exposed in the period between its transport from the donor to the recipient must not be injurious. Carrel has found that tissue may be transplantable after several hours and that ice chest temperature is suitable for preservation. Skin is still transplantable after an hour or more in gauze moistened with saline, at room temperature. Preservation in chemicals has not been satisfactory save in the case of blood corpuscles, in which instance formolized cells are still useful after several weeks. That such blood cells operate in all ways as living cells has not been determined, but there is no doubt that they serve for interchange of gases. Transfusion, however, does not represent permanently successful transplantation, since the cells are incapable of multiplication. Nevertheless, Ashby has shown that they may survive for more than thirty days, and Wearn, Warren and Ames found that such cells survive for an average of eighty-three days.

The fact that chemical conditions must be nicely adjusted is indicated by the failure of heterografts and the relatively higher degree of success of autografts over homeografts. The fact that blood transfusion is successful only with properly adjusted blood groups is due in large part to the action of isohemagglutinins and isohemolysins. Although Ingebrigtsen found, as the result of animal experiments, that interagglutination has no influence on transplantation of arteries, it has been indicated by Masson and conclusively demonstrated by Shawan that skin grafting is successful according to the same rules as hold for blood transfusion. That the failure of skin grafts from antagonistic donors is due to isocytolysins has not been conclusively proven although it is highly probable; that other chemical adjustment plays a part must also be considered. The chemical factors probably reside both in the transplant and the host.

That success may depend upon functional need for the transplant has been emphasized by numerous investigators, and this may be in some measure due to chemical influences. Salzer and also Halsted found that thyroid transplants do better in thyroidectomized animals. Halsted found that the same principle applies to parathyroids. This, however, is contradicted by the work of Loeb and Hesselberg on the thyroid. Marine and Manley found that spleen grafts do better in splenectomized animals than in others, and it is probable that the demand for function has at least some influence on transplantation. Marine and Manley also found that thyroid grafts do better in iodized animals than in normals. Jores maintains that muscle transplants do better if there be need for muscle function, but Saltykow pointed out that his success was probably due rather to conditions of the operation than to functional demand.

There is little doubt that the better the supply of blood to the transplanted part the greater the chance of success. An index of this is the success of Joannovics in transplanting parathyroids into blood vessels, and the importance of vascular supply is demonstrated in innumerable other experiments. Carrel's

success with transplantation of entire organs is dependent upon maintenance of circulation. That nerve supply is of importance is indicated by the fact that innervated muscle appears to do well, but that it is essential is certainly not proven.

The behavior of transplants varies with different tissue but as a rule there is a certain amount of necrosis of parts of the transplant. Some of the cells, however, retain sufficient bioplastic energy to survive and proliferate. The transplant sets up reactive processes in the host just as do foreign bodies, so that new vessels and connective tissue penetrate to support and nourish. Unsuccessful transplants undergo necrosis, and are either encapsulated or disappear, to be replaced by organization and cicatrization.

There is no doubt that transplanted tissue may continue to functionate.

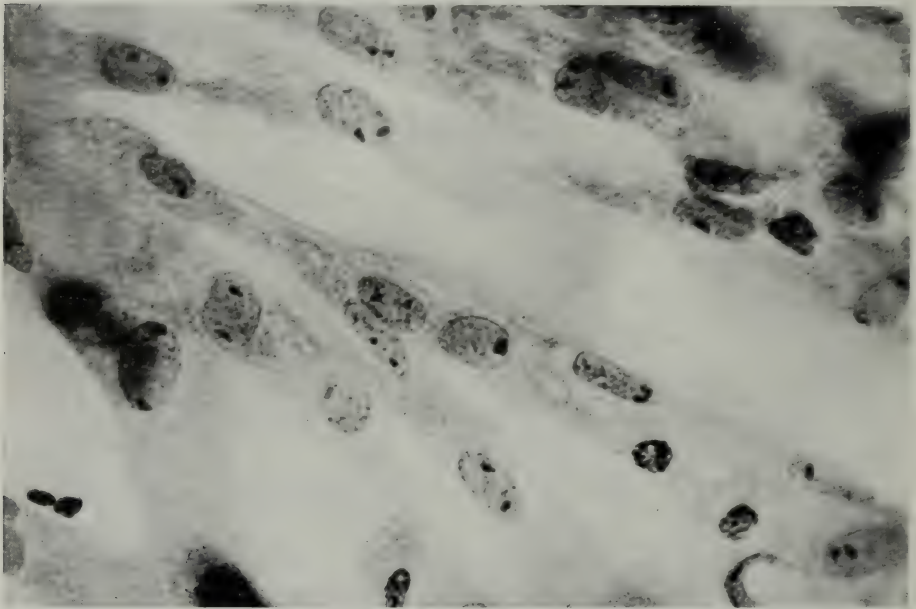


FIG. 135—High power photomicrograph of connective tissue culture. Note mitotic figures. From Carrel and Burrows, *Jour. Exper. Med.*

The maintenance of thyroid and parathyroid function has been indicated above. Ovarian function may be maintained in every way, as pointed out by Guthrie and others. Carrel's transplanted kidneys secreted normal urine. Transplanted nerves, muscle, periosteum, bone, pancreas, and other tissues may continue to function. Discussion of the transplantation of individual tissues and organs is too extensive to be included here, but is to be found in reviews such as that of Goldzieher and Makai, and the more recent article by Goodman.

The term parabiosis indicates the anatomical and physiological union of two animals of either the same or different species. Double monsters demonstrate the condition as it occurs naturally. Experimentally, it has been found practicable in animals of the same (Rous) or closely related species such as

mouse and rat (Lambert), but in different species the death of one or the other individual soon supervenes. As a method of experimental work the condition has been utilized to study immunity, function of kidneys and pancreas, and other problems, all of which are considered in detail by Goldzieher and Makai.

Tissue Culture. Explantation.—The fact that tissues may survive outside the body has long been known and utilized in the study of function. That cells may grow and multiply, *in vitro*, an entirely different proposition, has developed in the present century. It is true that in 1897 Leo Loeb was able to cultivate and observe the multiplication of epithelium upon culture media and thus is the pioneer in this field, but his method is apparently not widely applicable. It remained for Harrison, in 1910, to adapt, as he says the tissue isolation method of the embryologist and the hanging drop method of the bacteriologist, in order to study the growth of nerve fibers. The method was soon elaborated and extended by the work of Burrows, Carrel, Lambert, Hanes, L. Loeb, the Lewises, Fischer, Strangeways and others. At first applied to the general biological problems of cell multiplication and growth, it was soon extended to include physiological, pathological and immunological fields. Thus, there is definite information that calcium and potassium ions, maltose, dextrose and certain protein decomposition products favor multiplication and growth, and that the presence of a solid supporting framework, such as a net work of fibrin, is of importance although not absolutely essential. It is known that certain cells may be kept growing outside the body for long periods, as for example the Carrel connective tissue culture which has passed through more than 1800 generations in more than ten years (Ebeling). Burrows showed that embryo heart muscle can grow and multiply *in vitro*, and that the primary and descendant cells retain an intrinsic capacity for rhythmic contraction over several weeks. Cells may grow in plasma of widely different species, and certain features of their metabolism have been studied. It has been found that most cells in culture exhibit ameboid movement, and there is reason for believing that surface tension phenomena are of great importance in cytoplasmic division.

Foreign body giant cell formation has been shown by Lambert to be due to fusion of large mononuclear cells, possibly of endothelial origin, and not participated in by fibroblasts. The work of Lambert indicated that the common presence of fat globules in culture cells depends upon fat in the medium and is roughly proportional. Foot, however, thought he could see direct transformation of cell granules into fat, and Lewis maintained that fat is formed in cells growing in fat free media. Nasu is doubtful that the material in the cells is fat and found that cells living, or perhaps vegetating, in salt solution show no such globules. Nevertheless, the work in general indicates that some cellular



Fig. 136—Isolated culture cells containing fat globules.

endogenous mechanism can elaborate fat. Lambert was able to demonstrate that sarcoma cells show atypical mitosis in culture as compared with normal mitosis in non-tumorous cells, that sarcoma cells are more readily affected by heat, and Drew has found that the stroma of tumors behaves more like embryonal than like adult cells. Lambert studied the movement of tumor cells and estimated that by this process alone, tumor cells could migrate from the breast to the axillary lymph nodes in six to eight weeks. It has been shown that plasma from sarcoma-immune animals does not inhibit growth, thus indicating that tumor immunity does not reside in the plasma. Carrel and Ingebrigtsen have demonstrated that cells in vitro are capable of producing specific hemolysins and Fischer has demonstrated increased resistance on the part of cells against injurious antigens. Lambert has shown that isohemagglutinins have no influence upon human cell cultures.

At first the work was limited to the use of cells from lower animals, embryo and adult, but was extended by Lambert to include human cells. Media capable of forming permanent fibrin nets were considered essential but later fluid and solid media were employed. Carleton draws attention to the relationship in cultures between connective tissue and other cells. The connective tissue seems to be an important factor in restraining unlimited cell multiplication and upholding differentiation. The field of work is now broadened by studies, notably those of A. Fischer who has succeeded in growing intestinal segment with multiplication of all elements and the secretion of mucus by the epithelium. The extent and possibilities of this mode of investigation cannot be predicted, but it seems likely that much light will be thrown upon the natural history of cell growth in health and disease.

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CHAPTER XII

TUMORS

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- APPENDIX. CYSTS.

Introduction.—Although the term tumor in its etymological sense signifies only swelling, the current usage requires more strict definition. Indeed a tumor, according to present conceptions, may be erosive and destructive in character and show no swelling whatever. Simply stated, a tumor is an autonomous, progressive, unlimited new growth without known cause or useful function. The definition, however, is open to further defining and qualifications. It is autonomous in that it has its own laws of growth, which do not necessarily harmonize with those of normal cell growth. Its autonomy is limited by the fact that it depends upon the host for blood supply and support. Being autonomous and deriving its nutrition from the host, it is essentially

parasitic in character. The type of cell in certain tumors and the general biology of growth, both in the host and in vitro, often suggest the characters of exogenous parasites. The new growth arises in preëxisting cells or tissues and is therefore an offshoot of either the somatic or germ cells. It necessarily resembles in cell character the cells from which it arises, but aberrations from type are frequent and often confusing. Inflammatory and other types of hyperplasia are new growths, but are limited and useful and show gross and microscopic characters sufficiently characteristic. The tumor is progressive in growth but not uniformly so, since periods of quiescence or even of regression may interrupt the continuity of progressive enlargement. As a corollary of the progressive growth must be the conception of unlimited growth, but the latter character is of course variable with the type of tumor and fundamentally restricted by the life of the host and its capacity for providing nutrition. Secondary changes such as inflammation and necrosis often seriously interfere with tumor growth. The growth is new not only in the sense of multiplication of cells, but also in the fact that the proliferation may show cell types not in absolute conformity with those from which it originated. The cells in tumors may function, as for example, in the formation of bile in liver tumors or the formation of a milky material by breast tumors; these secretions are without value to the host. Occasionally, instances are observed in which secretion is useful, as for example in the case of removal of thyroid tumor and the maintenance of thyroid internal secretion by secondary growths in other situations.

Although the exciting cause of tumors is not known, certain conditions can undoubtedly be looked upon as predisposing causes, such as repeated or prolonged irritation, trauma, age, etc. The common wart can be transmitted by a filterable virus, which has not yet been cultivated; the Rous chicken sarcoma is also transmitted by a filterable virus provided the ground for transplantation is properly prepared. These, however, are exceptions to the rule. Some believe that in both these instances, trauma and site of inoculation are of more significance than the virus, but the experimental evidence in favor of a specific virus is convincing to most students. Of considerable importance is the conception of tumors as local in character. It is true that they may become widespread in the body, but equally true that their origin is in one, or at most a very few, places.

Tumors have been known throughout the recorded history of man and are mentioned in the records of India about 2000 B.C.; other records appear in Egypt about 1500 B.C., and in the cuneiform tablets of the library of Ninevah. The writings of Hippocrates, Galen, those of the Middle Ages and Renaissance give excellent descriptions, but exhibit the fallacies of interpretation common to those times, and due to the existing ignorance of physiology and anatomy. Tumors are not confined to man, but appear to be of greater importance in human medicine than in that of domestic and wild animals. They are not unknown in invertebrates and many believe that certain nodular growths in plants should be regarded as tumors.

The incidence of tumors is of the utmost importance from the viewpoint of

public health. In 1917 the death rate from cancer was 81.6 per 100,000 of population. Symmers found a somewhat similar incidence in the necropsies at Bellevue Hospital; namely, that of 5155 patients coming to necropsy about 6 per cent. showed malignant tumors. The data given by F. L. Hoffmann show a somewhat similar rate of incidence wherever statistics are collected. The work of several investigators, notably Schereschewsky, points toward an increase in cancer mortality. Pearl indicates that in the United States the volume of immigration may influence the figures. Howard found no increase of incidence in Baltimore. Strong's larger analysis led him to conclude that the incidence of cancer is increasing slowly if at all. The question is to be regarded as still open. The economic loss due to death from tumors is extremely large, and the loss due to disability is incalculable. As will be indicated, there is little ground for assuming an infectious nature of tumors and there is thus no reason for isolation of patients. On the other hand, certain predisposing causes are well known and are preventable. Education leads to early submission for diagnosis, and early diagnosis vastly improves the chance of cure. Certain occupations may involve conditions which predispose; these conditions can be improved so as to lessen or eliminate the predisposing lesions. There is thus a large field for preventive medicine.

Classification of Tumors.—It is sometimes stated that the important feature of classification of tumors is the division into benign and malignant tumors, but as will be pointed out subsequently, this division can not be sharply drawn and only precise classification can be satisfactory to the worker who wishes exact information to guide his treatment and prognosis. Tumors, like tissues, are of more or less complicated structure, but as a rule have cell type or types which furnish a basis for classification. These cell types serve to identify a tumor in much the same way as they serve to identify a normal tissue. For example, skin is composed of epidermis and corium with its accessory structures. The papilloma is a tumor of epithelial character but is really more or less mixed, since it consists of a ramifying papillary supporting framework of connective tissue covered with stratified squamous epithelium. Other tumors, however, may be made up solely of one type of cell, as for example, the fibroma which is composed of fibrous tissue cells; nevertheless, these have a vascular supply and may even have nerves. Most of the classifications of tumors are based upon histological characters and are therefore morphological in nature. These may refer to the cell type of the tumor itself or to the original germ layer from which the type cell originated.

The earliest of the modern classifications is that of Virchow, into histioid, organoid and teratoid. The histioid tumors include those in which the growth is composed almost entirely of one cell type, as for example the fibroma. Such a tumor may be regarded as arising from a cell with unipotential character, i.e., with a capacity for forming but one type of cell. The organoid tumors are made up of more than one type of cell and in a general way more or less reduplicate organ forms, as for example the adenoma with its atypical glandular acini, supporting connective tissue and vascular supply. If such tumors arise

from a single cell, that cell must be multipotential. The teratoid tumors include such tumors as arise in certain situations, particularly along the urogenital tract, and produce tissues corresponding to two or more layers of the embryo. The teratoma of the testicle may contain cartilage, intestinal type of tissue, skin-like tissue, nervous tissue, etc. If such a tumor arise from a single cell, that cell must be, like the ovum or the cells of the blastomere, totipotent. This classification can be made to include all tumors, but in many instances is difficult to apply.

Although several classifications such as that of Adami, are based upon most thoughtful study of the biology of tumor growth, nevertheless, those which are most widely employed represent either the original, or some modification of, the classification proposed by Borst. This is based upon the histology of the tumor. Thus, we recognize connective tissue tumors, epithelial tumors and mixed tumors. The term connective tissue in this sense is extremely broad, since under it are grouped tumors composed of various types of true connective tissue, those of muscle, those of various types of nervous tissue and those of endothelium.

The nomenclature of tumors is somewhat confused and although that which we adopt cannot be regarded as exact in etymology or descriptive character, yet it is widely employed and can hardly be altered except by making it ponderous. As will be seen subsequently, there are many tumor-like conditions which do not correspond to the definition of tumors given above. In order specifically to indicate that a true tumor of independent growth is meant, the term blastoma is often used. Indeed certain authors, notably Mallory, use the suffix blastoma in nomenclature so as to indicate precisely the nature of the condition, as for example, fibroblastoma, lipoblastoma, glioblastoma, etc., instead of fibroma, lipoma, glioma. There are also tumor-like conditions, which may become blastomatous, representing faults in development. Thus, adrenal cortex may be found in the kidney. This separation of tissue from its proper site, when looked upon as a tumor-like mass is called a choristoma, and may readily take on independent growth to constitute a choristoblastoma, of which group the hypernephroma is an example (Albrecht). Sometimes tissues may show faulty development, which leads to the presence of tumor-like masses. Thus, the capillaries of the liver may fail to undergo regression in a certain area and there remains the hemangioma of the liver (Moise). This type of condition is referred to as hamartoma and may give rise to independent growth to form the hamartoblastoma. Tumors may arise at points of junction of embryonal folds or may originate in embryonal cells which have not differentiated for proper development of the organism.

The following arrangement is one of convenience and represents the Borst classification somewhat modified. It follows in some particulars that of Ewing. It serves as a guide both to classification and nomenclature. Any classification at the present time is emphatically one of convenience and cannot be regarded as final. As in all fields of pathology, a system based on cause is the only one which will have both practical and academic value. Until the etiology of

tumors is determined and elaborated, no classification can be regarded as fully satisfactory.

A. The Connective Tissue Tumors.

I. Connective tissue as a type.

1. Fibroma—fibrous connective tissue.
2. Chondroma—cartilage.
3. Osteoma—bone.
4. Myxoma—mucoid tissue (like Wharton's jelly).
5. Lipoma—fat.
6. Angioma—vessels.
 - a. Hemangioma—blood vessels.
 - b. Lymphangioma—lymphatic vessels.
7. Lymphoma—lymphoid tissue.
8. Chordoma—notochord.

II. Muscle as a type.

1. Leiomyoma—smooth muscle.
2. Rhabdomyoma—striated muscle.

III. Elements of the Nervous System as a type.

1. Glioma or neuroglioma—neuroglia.
2. Neuro-epithelioma—neuro-epithelium.
3. Neuroma—nerve fibers and cells.

IV. Endothelium as a type.

1. Endothelioma—endothelium.
 - a. Angio-endothelioma.

V. Sarcoma—malignant connective tissue tumors.

1. Immature forms—of more or less undifferentiated cells.
2. Mature forms—malignant tumor with differentiated parts like any of the benign forms mentioned above.

B. The Epithelial Tumors.

- I. Papilloma—of surface type of epithelium upon a supporting connective tissue.
- II. Adenoma—glandular epithelium upon a supporting connective tissue.
- III. Epithelioma—epithelium usually of surface type, in atypical arrangement.
- IV. Cylindrical Cell Carcinoma—cylindrical epithelium from glands or surfaces, in atypical arrangement.

C. Mixed Tumors.

- I. Simple Mixed Tumors—made up of more than one type of tumor tissue, arbitrarily including monodermal, e.g., osteochondroma, and bidermal, e.g., mixed tumors of parotid and of kidney.
- II. Teratoma—made up of tissues differentiated to represent three layers of embryo, and therefore tridermal.

This outline will serve as a basis for a systematic study of tumors. Of the groups indicated, the sarcoma, the epithelioma and the carcinoma are referred

to as *malignant*. This term, however, is only relative and refers to the capacity of the tumor for direct invasion and destruction of surrounding tissues, for setting up secondary growths of the same character in other situations, for recurrence after removal, and perhaps for production of absorbable products which have a poisonous or other deleterious effect upon general bodily metabolism. Tumors which do not show these characters are commonly referred to as *benign*. This term, although it has a definite clinical and pathological significance, is only relative, since no type of tumor can be regarded as absolutely devoid of harmful effect. Truly benign tumors have none of the characters ascribed to malignant tumors, but may produce harmful effects by pressure on important organs which if long continued will lead to pressure atrophy; hollow organs may be obstructed, secretions may be dammed back, nerve trunks and blood and lymph vessels compressed, etc. There are certain tumors, usually classified as benign, which are not strictly so because they exhibit at least one character ascribed to malignancy. For example, the chondroma is likely to recur after removal. The glioma is directly invasive and destructive and frequently recurs after removal. Exceptionally, it may even metastasize. Thus, it has several characters of malignancy, but its structure is so much like other tumors which are benign that it is usually so classified. There is, then, no sharp line of exact differentiation between benign and malignant tumors.

Transformation of Benign to Malignant Tumors.—Owing in large part to experimental studies and in part to examinations of human tumors, many investigators now doubt the transformation of benign into malignant tumors. Ewing regards true transformation of this sort as a rare occurrence in the natural history of tumors. Nevertheless, the opinion is widely held that such transformation can and does occur. Studies of thyroid tumors by Graham indicate that many of the cancers originate in preëxisting benign adenomata. The apparent transformation of the fibromyoma of the uterus into sarcoma seems well established, as is true also of fibro-adenoma of the breast into cancer. The pigmented mole of the skin, after remaining quiescent for many years may suddenly become malignant, particularly after traumatic injury, but there is a reasonable question as to whether the mole should be classified as a tumor or as an embryonal misplacement. The opponents of the idea of malignant transformation suppose that the tumor is malignant in character from the start, and is only apparently benign, or that a new malignant tumor originates within the older benign tumor. Williams, however, is of the opinion that benign tumors are less likely to become malignant than is malignancy to arise in tissues not otherwise tumorous. The question has great practical significance, because if benign tumors cannot become malignant, their removal and diagnosis can be followed by an unqualifiedly favorable prognosis. If transformation be regarded as possible, such a prognosis cannot be made unless the surgeon is positively sure that all the benign tumor has been removed. Until the question can be definitely settled, and until the differentiation between benign and early malignant tumors can be placed on a satisfactory basis, the best interests of patients will be served by regarding all tumors as potentially malignant.

Modes of Origin.—In a general way it is said that tumors may originate from one group of cells and are thus *unicentric*, or originate from several groups of cells and are thus *multicentric*, in origin. Virchow propounded the law *omnis cellula e cellula*, which placed pathology upon a rational basis, and as applied to tumors indicates that their cells originate from similar cells. This does not necessarily imply that a tumor originates from a single cell; such may be the case but it is generally believed that the origin is in cell groups rather than individual cells. Study of the mode of growth of tumors leaves little



FIG. 137.—A large fungating cancer of the esophagus opposite the cricoid cartilage.

doubt that most tumors are unicentric in origin. Nevertheless, multicentric origin is not rare. This may be observed in tumors in an organ, tumors in paired organs and tumors in organ systems. Thus, the stomach may show multiple polypoid adenomata, several of which may undergo malignant change. It is believed that certain primary cancers of the liver show multiple centers of origin. By reconstruction of serial sections, certain cancers of the breast and of the lip have been shown to originate from several foci. Neurofibromata, in the form of multiple neurofibromatosis (von Recklinghausen) appear practically simultaneously in various parts of the skin. Paired organs such as the breasts, testes, and ovaries may show simultaneous in-

volvement by the same sort of primary tumor. Excellent instances of multicentric origin in systems are offered by the lymphosarcoma, which as a rule affects a chain of lymph nodes rather than a single node, and by the multiple myeloma which originates in several centra in the marrow of one bone or of several bones.

In addition a patient may be the victim of more than one type of tumor. This is common in women, in whom fibromyomata are so frequent that their concurrence with other tumors of the uterus or of other organs is often noted. We have observed numerous instances of more than one type of tumor, including one case with cancer of the stomach and hypernephroma of the left kidney.

Certain statistics show 0.5 to 1.0 or more per cent. of concurrence of different types in tumor cases. Such figures are low. In a series of fifty-five tumor cases, Symmers found twenty-two with more than one type. This proportion is doubtless high. The occurrence of multicentric tumors is possibly to be attributed to a stimulus of some sort operating in different foci. The same may be true of multiple tumors of different types, the difference being due in part to the various types of cells in the different organs involved.

Originating in a single cell or in a small group of cells, there remains the question as to whether or not the neoplastic stimulus or process can extend through neighboring normal cells. Cells near tumors may exhibit changes designated as precancerous, or pretumorous. Hyperplasia and metaplasia may resemble tumor growth very closely, and cells may proliferate in such a way as to indicate that further multiplication will lead to true tumor growth. This phenomenon appearing near a growing tumor suggests that the stimulus which has operated upon the cells already tumorous is involving neighboring cells, which subsequently will constitute part of the tumor. If this be true, the extension of a tumor is not solely due to multiplication of the original cells involved. Such involvement of neighboring cells in the process may be due to an extension of the causative factors from one cell to another, and is not necessarily due to contact of tumorous cells with non-tumorous nor to the migration of a parasitic cause. This hyperplastic or precancerous state is closely similar to collateral hypertrophy of cells, in which neighboring cells show enlarged and hyperchromatic nuclei, and cell multiplication. Thus, the connective tissue near a cancer may resemble sarcoma and in rare instances become definitely sarcomatous. In certain adenomata, neighboring glands may show such hyperplasia, and this condition is differentiated from an extension of the tumor only with difficulty.

Mode of Growth.—The most important and common method of tumor growth is by cell division. Although direct division may be observed, mitotic division is of far greater frequency and importance. Direct division may be by budding or fission of the nucleus. Mitosis is usually typical but may show many variations from the normal. The usual bipolar mitoses may show hyper- or hypochromatism or may show such large forms as to be called giant mitosis. Distinctly abnormal forms include the asymmetrical and multipolar mitoses. In the former a much larger number of chromosomes may migrate toward one centrosome than the other and correspondingly the divided forms may be either hyper- or hypochromatic. In the multipolar mitoses the centrosome apparently divides into several fragments with irregularly placed multiple attraction spheres, of even or uneven number. The resulting asters are not necessarily equal in content of chromosomes. Abortive mitosis in which there are abnormalities of polarization, irregularities in chromosomes and degenerations of cytoplasm, are seen particularly in degenerative conditions in tumors. The degeneration of nuclei may also produce figures which resemble the formation of chromidia. Careful studies have shown that division of tumor cells may exhibit a reduction in the number of chromosomes so as to resemble maturing

sex cells. Boveri offers the suggestion that the reduction of chromosomes is responsible for the unlimited multiplication in tumor growth. Johan thinks that the nuclei of malignant tumors contain an increased amount of nucleolar substance, which sometimes shows alterations in staining character. This, however, is probably not constant and its significance is by no means clear.

Interpretations of the variations in cell division have led to the suggestion that the process resembles that in protozoa. The reduction of chromosomes suggests that the tumor cells have reverted to and possess the characters of sex cells. These hypotheses are not sufficiently well supported to justify acceptance. The variations in chromasia of the nuclei and the abnormal mitoses have been regarded as indicating an increased power of proliferation, with concomitant loss of differentiation, a condition called anaplasia. The reverse conception,

that the tumor cell first loses functional capacity and thus gains in power of growth is called kataplasia. Certainly, both changes exist but which is primary is still a problem.

Although the growth of tumors is generally progressive, it may not be continuously so and may even show apparent retrogression. It continues in most cases until removal, or the death of the host. As with other live tissues, tumor cells may be cultivated on artificial media through many generations, extending over years. The reason for the death of the tumor with the death of the host is simply the removal of the source of nutrition. The growth of the tumor from the original group of cells may follow in a general way two

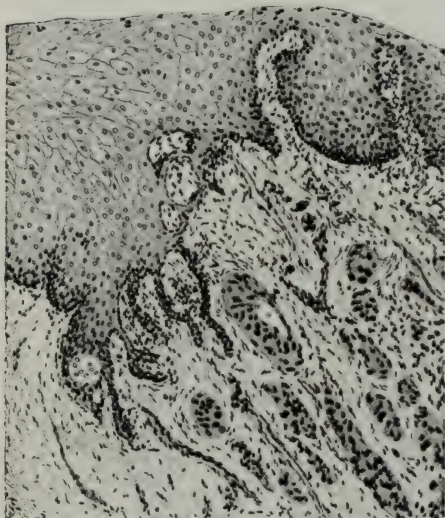


FIG. 138—Carcinoma of the esophagus showing downward penetration of interpapillary epithelium.

different modes. It may be by expansion of the original small mass, whereby the principal growth appears in the center of the tumor, often referred to as a centripetal type of growth. Enlarging in this fashion, the tumor tends to push aside the surrounding tissue and is more readily encapsulated than is the case with the opposite type of growth. Malignant tumors grow by multiplication more particularly of the peripheral cells. These cells grow into and through the surrounding tissue, destroying the tissues as the growth progresses. This is described as infiltrative or centrifugal in type. Centrifugal growth is more rapid than centripetal. Thus, the malignant tumors are likely to grow more rapidly, are distinctly more destructive than are the benign tumors, which, by the very nature of their growth are not infiltrative and are readily encapsulated by the surrounding tissues.

The shape of tumors is fundamentally spherical but surrounding conditions may alter the shape materially. Thus, tumors in the pelvis or in the skull may

be of various forms. Tumors on surfaces may be sessile flat masses, or pedunculated spheroids. The mode of extension may alter the form; tumors of the intestines may form rings about the gut and tumors in the spinal canal may be elongated.

Retrogressive Processes in Tumors.—The cells and tissues of tumors are subject to the same sort of degenerative and other retrogressive changes as are observed in tissues not tumorous. Tumors, for example, furnish some excellent examples of pigmentation. Passive hyperemia within tumors may lead to the deposit of hemosiderin and other blood pigments. The melanotic sarcoma is an example of the formation of pigment by the chromatophores. Tumors of the body may become pigmented with bile as a part of general jaundice. Tumors of the liver may actually form bile, and be the seat of bile pigmentation similar to that seen in the liver as the result of obstructive jaundice. Cloudy swelling is often present in tumors. Fatty degeneration is very common in cancer and may appear in sarcoma. The exact cause cannot be definitely stated but the change probably occurs under much the same conditions as in other cells. The lipoma is a tumor made up of fat cells, anatomically and chemically like fat elsewhere in the body, but as a rule does not furnish fat for utilization in the general body metabolism (Wells). Hydropic infiltration is present in the form of an intracellular edema and depends upon the same conditions that produce edema elsewhere. In tissue spaces where tumor cells are desquamated and fluid is present, the isolated cells may imbibe the fluid freely. Simple hyalin is frequently found, both as an intracellular form and as a connective tissue deposit. The latter is commonly seen in old fibromas and in the capsules of many of the benign tumors. Intracellular hyalin is fairly common. In the squamous epithelioma hyaline bodies, of the nature of keratin, are frequently present; these were looked upon as representing some stage in the development of a parasite, but this view has now been completely discarded. Amyloid is sometimes observed, and it is to be remembered that invasive and destructive tumors, particularly cancers, may cause general deposits of amyloid. Colloid is to be found in tumors which originate in the thyroid gland or in the pituitary body, but the iodine content may not be so constant as in the original normal gland structure. Except for tumors of this sort, it seems unlikely that true colloid occurs, although various other forms of hyalin may exhibit the brown, homogeneous appearance of colloid. Mucinous degeneration appears particularly in epithelial tumors. The carcinoma of the intestinal tract, particularly that seen in the large intestine, is likely to produce fairly large amounts of mucus, which gives the tumor grossly a gelatinous character. As the tumor advances, cellular degeneration may be very marked and the vascular spaces filled almost entirely with mucin. Mucoid material is seen particularly in the myxoma where the fibrils are separated by basophilic material. Mucoid degeneration may appear in a considerable number of connective tissue tumors. Pseudomucin is found in certain tumors. In cystic disease of the ovary it is not uncommon to find fairly large cysts which contain a gelatinous, homogeneous material, pseudomucin, which has some of the properties of mucin but stains

with the acid dyes. Glycogenic infiltration is more common in those tumors whose cells are by nature more nearly of embryonic type. Thus, the teratoid type of tumor is likely to be rich in glycogen. On the other hand, those tumors which are made up of cells and tissues more nearly resembling the adult type, are likely to show little or no glycogen.

Circulatory disturbances are fairly common and are particularly pronounced in those tumors which are pedunculated. Twisting of the pedicle may lead to obstruction of the outflow of blood so as to induce considerable passive hyperemia. Edema is also common in this type of tumor. It is not to be assumed, however, that all edema seen in tumors is necessarily of mechanical origin, because tumors may be extremely edematous and show relatively little passive hyperemia, as for example, the nasal polyp. Hemorrhage is common in the richly vascularized sarcomata and occurs in other tumors. Passive hyperemia, trauma, degeneration or necrosis in the tumor with involvement of vessel walls and inflammation, may produce hemorrhage. Necrosis is common more particularly in rapidly growing, malignant tumors. It may be the result of such rapid growth that the blood supply is inadequate, of passive hyperemia or of complete stasis due to occlusion of vessels. Such occlusion may be due to pressure by surrounding viscera or bones on the growing tumor mass, to thrombosis or embolism of blood vessels, to rupture of vessels, to inflammation, or to twisting of the pedicle of pedunculated tumors. The carcinoma as a rule is a poorly vascularized structure, and as the growth proceeds with considerable rapidity, the circulation is not sufficient to maintain life in the cells. Therefore, the central part of such tumors is frequently necrotic. The sarcoma is usually a richly vascularized structure, but in spite of this vascularization, necrosis, apparently as the result of inadequate blood supply, is often seen. Whether or not certain ferments are present, which may lead to necrosis, is open to question. There is no doubt that tumors contain considerable amounts of the products of autolysis, but there is little reason for believing that tumors contain larger quantities of autolytic or oxidizing enzymes than do normal cells. Gangrene may occur in tumors, especially those eroding into the alimentary canal. Tumors are rarely, if ever, the seat of infection by the organisms of the specific granulomata. Suppurative and other simple types of inflammation are observed in tumors when bacteria gain access. This, of course, is more common where tumors erode upon surfaces. Occasionally, a tumor may be invaded by another malignant tumor. Thus, the uterine fibromyoma is not rarely invaded by cancer of the uterus.

Inflammatory Reaction.—The tissues in the neighborhood of tumors very often show inflammatory reactions of subacute or chronic grade. It is unusual that acute exudative inflammation appears except as the result of infection, but vascular dilatation is not uncommon about the margin of tumors. The subacute infiltration of cells occurs rather in the neighborhood of invasive tumors than in the neighborhood of benign tumors. Thus, in the margin of cancer or sarcoma there is often found a rich infiltration of lymphoid cells, associated with smaller numbers of plasma and endothelial cells. In the neighborhood of

malignant tumors in certain situations, as for example, in the cervix of the uterus and the large intestine and sometimes elsewhere, there may appear a rich infiltration of eosinophilic cells, mononuclear and polymorphonuclear. There is usually an associated infiltration of the cells mentioned above, but sometimes the eosinophiles quite outnumber the other cells. The cause of this subacute reaction and lymphoid infiltration is not known. In certain respects it resembles that to foreign bodies, and it may be that death of invaded tissues may stimulate the reaction. It is also possible that necrosis within the tumor leads to the reaction in the surrounding tissues. It is further possible that the presence of the tumor itself, being of parasitic nature, may be sufficient to institute the reaction. That products absorbed from the tumor growth have an irritative influence upon surrounding tissue is still problematic. The relation of this reaction to resistance will be discussed subsequently. The more chronic type of inflammation, consisting of an overgrowth of connective tissue, is especially prominent around the benign tumors, but may be seen in the form of partial and incomplete encapsulation around malignant tumors, more particularly the sarcoma. That the capsule of benign tumors is entirely the result of chronic inflammation in the neighborhood is not true. Certainly in those tumors made up largely of fibrous connective tissue, such as fibroma, there is little doubt that the tumor itself contributes a considerable part of the capsule. In these benign tumors, there is little reason for believing that necrosis, absorbable products, or local death of the tissues of the host institutes the reaction. Such deposition of connective tissue commonly occurs in areas where pressure is exerted, and it is highly probable that the chronic reaction to this type of tumor is due to the pressure instituted by the expansive or centripetal type of growth.

Functional Activity in Tumors.—As a general rule, the tumor exhibits no evidence of the functional activity of the cells from which it originates and of which it is built up. The capacity of epithelial and endothelial cells to cover surfaces may be seen in the tumor cells; they may extend to a certain degree over abraded and granulating surfaces. Definite ameboid activity of living tumor cells is only rarely observed, but phagocytosis by tumor cells, of dead tumor cells, of erythrocytes, of bacteria, of tissue fragments, dead leucocytes, bile, crystals of various kinds and foreign bodies is not uncommon. The capacity of individual cells to retain certain types of function is not uncommon. For example, the melanotic tumors continue to form melanin but this capacity is likely to be lost as anaplasia, that is, loss of function with increased proliferative capacity, becomes more marked. Cells originating from the adrenal body and constituting the hypernephroma continue to contain lipid material, and the fat cells of the lipoma contain considerable amounts of fat. There is little reason for believing that adrenalin is produced. Glandular cells may produce external secretions. For example, the carcinoma arising in mucous glands of the intestine may produce very large amounts of mucin, but this mucin is probably not secreted in any considerable amounts into the gut. Adenomatous and adenocarcinomatous tumors of the liver have been observed to form bile, but this again is probably not available

for intestinal function. Occasionally, adenomata of the breast show, within the acini of the tumor, a material which resembles fairly closely a colostrum-like milk. The study of internal secretions of tumors originating from the endocrine organs offers the same difficulty as the study of internal secretions in general. Nevertheless, tumors of the pituitary glands may be associated with what is believed to be an exhibition of over function in the form of gigantism or akromegaly. One case is recorded in which tetany followed the removal of a tumor of the thyroid gland, but disappeared upon the development of metastasis, thus indicating that the metastasis took up the internal secretions of the original thyroid gland. It may be said in summary that most tumors exhibit no function whatever; that some may exhibit overfunction and that others

may exhibit a minor degree of function of little, if any, use to the body.



Fig. 139—Intravascular tumor growth—a tumor thrombus.

Stroma.—The connective tissue supporting framework of tumors appears in the form of bands of white fibrous connective tissue, and also in the form of fine fibrils interspersed between the tumor cells. The dense stroma may indeed proliferate in such a way as to divide the tumor into alveoli. The origin of the stroma differs with different types of tumor. The benign tumors usually supply all their own connective tissue supporting framework. The experimental study of tumors has shown very clearly that the invasive malignant tumors derive most of their stroma, if not all, from the host. In the various forms of cancer the stroma is usually fairly abundant, but in most of the sarcomas there is a relatively small supply of stroma; the latter are in great part made up of connective tissue of one sort or another,

and require very little supporting framework. The epithelial tumors, however, grow very largely by proliferation of epithelial cells and these require a supporting framework, which as has been said, is furnished by the host. Yellow elastic tissue is destroyed as tumors invade, but masses of original elastica may be found remaining in the tumor areas. It has not been proven that yellow elastic tissue proliferates in the course of tumor growth. As anaplasia increases in tumors, the connective tissue growth is likely to decrease. Therefore, rapidly growing tumors and their metastases may show little or no stroma.

In certain tumors it is possible that the entire connective tissue supporting framework is simply a residuum of the original supporting tissue in the area invaded. Connective tissue may proliferate because of two important mechanisms. The first is a reactive, inflammatory overgrowth of connective tissue,

seen as a part of the general inflammatory reaction to tumor growth. The other is in the form of a desmoplastic activity of the tumor cell, a propensity to stimulate hyperplasia of connective tissue. As has been mentioned before, collateral hypertrophy of the surrounding tissues may occur in the course of tumor growth. Desmoplastic activity is probably somewhat different from this, in that the proliferation is confined particularly to the connective tissue. This is well illustrated in the scirrhus carcinoma, where well marked connective tissue hyperplasia goes hand in hand with the epithelial growth. Metastases from such tumors frequently show quite as much connective tissue hyperplasia as in the original growth, and this is interpreted as indicative of desmoplastic properties on the part of the epithelium. This connective tissue growth may be of importance to the host and lead to the ultimate regression or disappearance of the tumor. As a rule, however, this happy outcome is not observed. An important question is as to whether or not the stimulating powers of tumor growth may influence the connective tissue to take on malignant properties itself. It is not rare to find in association with cancers, a growth of connective tissue which is so strikingly like that of sarcoma that many have considered that the two processes coëxist, the one secondary to the other. Experimental work with cancer has shown that during the course of multiple transplantations of a cancer, a sarcomatous growth has appeared. These observations are highly suggestive, but it cannot be considered that at the present time desmoplastic or other influence is so great as unquestionably to have led to sarcoma.

Blood Vessels.—Numerous studies have suggested that local alterations of blood vessels are responsible for the growth of the tumors. It can safely be said, however, that these are not conclusive and that there is little reason for believing that tumor growth depends upon primary changes in the blood vessels. It is true that arteriosclerosis, phlebosclerosis, thrombosis, and other changes may be observed in the neighborhood of tumors, but there is much reason for believing that these are secondary rather than primary. In general, the supply of blood vessels to tumors follows the same laws as for the



FIG. 140—Cancer growing in a blood vessel and in surrounding perivascular lymphatics.

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connective tissue stroma. There can be little doubt, however, that the sarcoma furnishes much of its own vascular supply, either in the form of minute tissue spaces or small capillaries which communicate with vessels provided by the host. The capacity of blood vessels to form new elements is very great, and it is possible that the new formation of blood vessels seen in tumors may be regarded as part of the induced inflammatory reaction. The blood vessels in tumors differ from those of the host in that they are likely to be more tortuous and less likely to show regular dichotomous branches. Distension of overlying veins is very common in case of sarcoma and may be seen in other tumors. This is probably due in part to the compressing influence of tumor growth upon veins of the surrounding tissues.

Nerves are sometimes found in tumors, but probably represent original nerve fibers. Save for the special tumors of nerve tissues, they play little part in tumor growth.

Characters of Malignant Tumors. Invasion.—It is probable that nearly all tumors begin originally as a somewhat invasive growth. It is not uncommon for example, to find simple benign fibroma of the kidney, in the early stage, and similar tumors in the skin, which show no capsule or sharp delimitation whatever. Nevertheless, as these tumors increase in size, capsule formation becomes apparent. They then grow by virtue of proliferation of the more centrally placed cells. In a malignant tumor, however, encapsulation is rarely complete except in those instances where the tumor regresses. Experimentally, Loeb has shown that even in these instances, incision of the capsule may permit of renewed invasion by the tumor. The invasive character depends very largely upon the multiplication of the cells in the margin of the tumor. These grow through tissue spaces and into lymphatic vessels and even into blood vessels, and as they grow they destroy the intervening tissue. This destruction varies in different tissues. Parenchymatous tissues appear to be more readily destroyed than are connective tissues. Striated muscle is likely to be resistant and certain cancers may involve the perimysium long before the muscle fibers are destroyed. Smooth muscle is somewhat less resistant. Tumors may extend into nerve sheaths and invade richly between the nerve fibers before the latter are destroyed. The general tendency of invasive tumors is to extend along the lines of least resistance, but destruction of intervening tissues follows fairly rapidly as the tumor mass increases in size.

Metastasis.—Although there are exceptions, the general rule is that carcinomas metastasize through lymphatic vessels and sarcomas through blood vessels. This means that the metastasis of the former type of tumor is likely to be regional or local and of the latter widespread and distant. Two modes of dissemination through the lymphatics and blood vascular apparatus must be considered. The first is by direct extension and permeation of the tumor along these vascular tracts, and second is the dislodgment of tumor cells so that they float with the stream and are deposited at distant points. As a concrete basis for consideration of this topic, it may be said that cancer of the breast is likely to show secondary growth in the axillary lymph nodes; cancer of the tongue in

the sublingual and submaxillary lymph nodes; sarcoma of bones may show metastasis in the lungs and in other distant situations. It is obviously possible that cancer of the breast may produce growth along the lymphatics with final involvement of the draining lymph nodes. The same, of course, is true of cancer in other situations. Thus, metastases to humerus and femur occur at points near deep fascias, rather than at points where emboli from the blood stream are likely to be deposited.

Handley's studies of extension and metastasis of breast cancers throw much light on the general phases of the problem. He finds that the extension through the breast is due almost entirely to cells growing through the lymphatics, rather than to embolism, and although admitting that embolism to the axillary nodes may occur, is of the opinion that further extension from the nodes is rarely observed. Metastases from breast to neighboring skin and to neighboring and remote bones are due to permeation extension along deep fascial lymphatics. Visceral metastases are explained as due to extension into serous cavities and then, either to visceral surfaces by implantation of tumor cells in the serous fluids, or to the interior by involvement of lymph nodes and extension through lymphatic vessels to the deep parts of the viscus. Metastases to brain and skull are explained as due to permeation along lymphatics accompanying blood vessels to the part. Handley points out that although cancer may exhibit embolism through the blood stream, such emboli rarely lead to metastatic growth. There are, however, certain cancers which undoubtedly metastasize through the blood stream. Among these are the chorionepithelioma of the uterus and the primary cancer of the liver, which invade and produce tumor thrombosis in the blood vessels. Fragments of thrombi are carried as emboli and lodge in other parts of the blood vascular system to

produce metastases. Most of the sarcomata are so constructed that their cells form small vascular spaces or slits communicating with the vascular bed of the tumor, and there is thus access of cells to the circulation. Metastasis of sar-

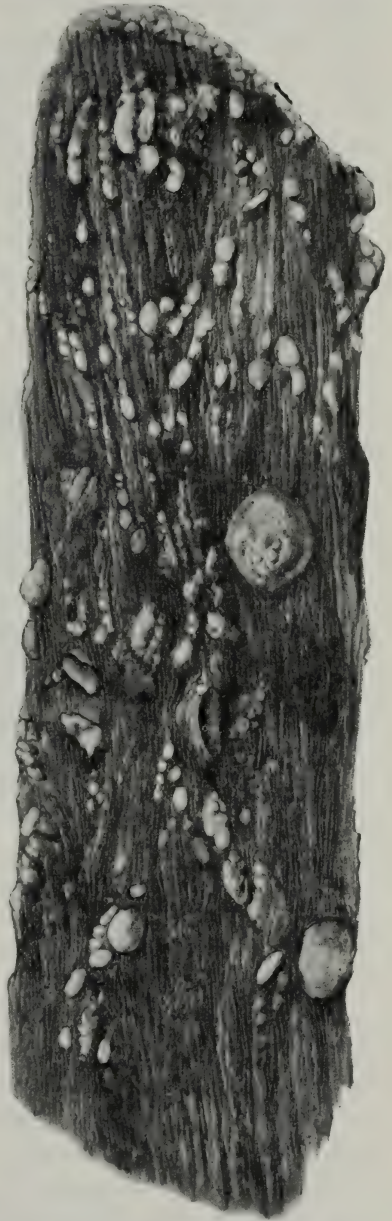


Fig. 141—Cancer nodules in pectoral muscle, secondary (metastases) from a cancer of the breast.

comata through the blood stream seems undoubtedly to be due to embolism of cells or cell groups. Direct extension of sarcomata along the blood vessels is often observed but does not explain remote metastases. It may be said in summary, that carcinomata metastasize through lymphatics and as a rule by direct extension or permeation, but metastasis due to embolism in the lymphatic or blood vascular system also occurs. Conversely the sarcomata metastasize by embolism through the blood vascular system, but may spread by direct extension through both lymphatic and blood vascular systems, and rarely by embolism through the lymphatic vessels. Malignant tumors vary, however, as to their capacity for metastasis, both as regards types of malignant tumors and individual examples of the same type. In a very general way, it may be stated that the more anaplastic the tumor, the greater is the chance of metastasis.

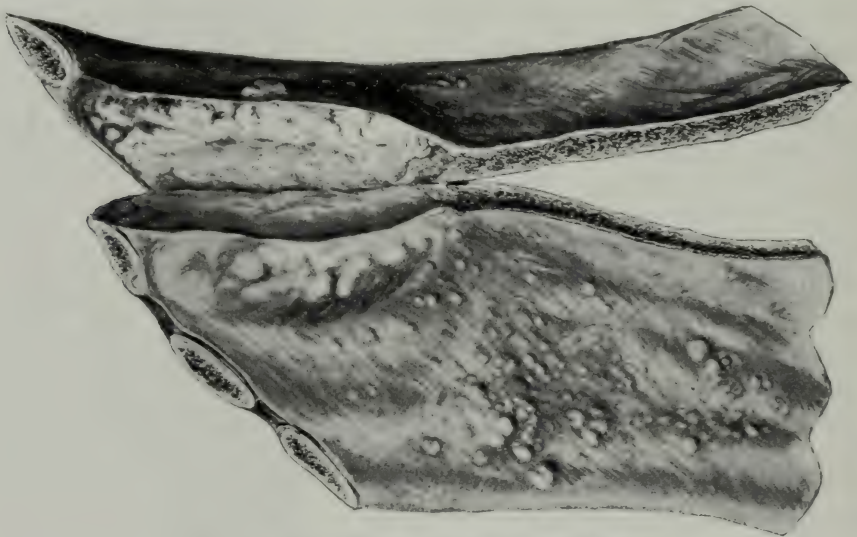


FIG. 142—Metastatic cancer in the pleura and in a rib.

There are certain peculiarities of metastasis which suggest that there may be selected fields for growth and that in certain instances the field may previously be prepared. There is little doubt that the involvement of lymph nodes by tumor growth is preceded usually by an acute hyperplastic lymphadenitis, in which the sinus endothelium multiplies and fills up these channels. That this is necessarily a purposive preparation of the field is doubtful since, as has been pointed out, the presence of the tumor leads to a certain amount of inflammatory reaction which may be reflected secondarily in the acute hyperplasia in the lymph nodes. That lymph nodes are involved in secondary growth of cancer, probably depends more upon the anatomical relationship than upon physiological characters of the nodes. On the other hand, certain tumors show curious disposition for growth in particular organs. An example is the fact that metastasis of the primary melanotic sarcoma of the eye is most frequent and attains greatest growth in the liver. This would seem to indicate that the liver

tissues offer favorable conditions for the growth of this particular tumor. The frequency of the involvement of the liver in secondary tumors originating in the stomach is easily explained by anatomical relationship. Conversely, the spleen is an organ which rarely shows invasion by carcinoma (Sappington). The spleen also frequently escapes even when there is widespread dissemination of sarcoma. This organ is richly vascularized and should be open to invasion by tumor cells floating in the blood stream. The spleen is frequently the seat of infarction, and it can therefore be assumed that foreign materials floating in the blood stream are likely to be deposited there. Unless tumor emboli follow different physical laws of circulation and deposition than do other emboli, it would seem that the spleen itself offers some resistance to tumor growth. This may be due to the rich content of lymphoid cells in the spleen, since the studies of Murphy, to be referred to subsequently, indicate that lymphocytes protect against tumor growth.

Symmers found that 74 per cent. of 298 cases of malignant tumors studied at necropsy, showed metastasis. Metastases occurred most commonly in lymph nodes, liver, pleura and lungs, bones and adrenals. He reëmphasizes the fact that organs commonly the seat of primary tumors are rarely the seat of metastasis and vice versa. Thus, as regards tumors, there are three groups of organs: (1) organs frequently attacked by metastases but rarely by primary tumors, e.g., lymph nodes, liver, lungs, pleura, bone marrow; (2) organs commonly the seat of primary tumors but rarely the seat of metastasis, e.g., stomach, breast, pancreas, prostate; (3) organs not commonly attacked by either primary or secondary tumors, e.g., spleen, heart, skeletal muscle, kidney.

Widespread dissemination of cancer, the so-called carcinomatosis, or carcinosis, may be due either to invasion of the blood stream by the primary growth, to the breaking of the secondary tumors of the lymph nodes into the neighboring blood vessels, or to invasion of the thoracic duct. The last complication may arise in connection with tumors of the stomach, pancreas, or other abdominal viscera, and before general dissemination occurs, invasion of the supraclavicular lymph nodes on the left side is likely to be noted (Virchow's node).

Transfer by Direct Implantation.—There is little doubt that tumors may be transferred from one part to another by contact. Thus, contact transference from one to another part of an organ has been reported in various situations, such as the urinary bladder, the vagina, vulva, stomach and from the kidneys into the ureters. Transfer from one lip to the other has been reported. The transfer of carcinoma of the esophagus to the stomach occasionally occurs. In all these instances it is difficult to exclude the possibility that the transfer is by way of the lymphatic tracts, and in certain cases of transfer from esophagus to stomach this mode has been definitely established. It is supposed that transfer to various parts of the peritoneum of a papilliferous adenocystoma of the ovary is by direct implantation of tumor fragments. This is probably true but cannot be regarded as finally proven because of the possibility that the dissemination is through the subperitoneal lymphatics. In the pericardium, the pleura and

the meninges, transfer appears to be more by direct extension along the surfaces than by distant transfer of tumor fragments. The transfer of malignant tumors from one individual to another in the human species occasionally occurs, as for example, the rare instances of transfer by coitus. Experimentally, such transfer may be accomplished in animals by rubbing tumor fragments upon abraded surfaces. In dogs the transfer of the peculiar infectious lymphosarcoma by coitus is well established.

Cachexia.—The general disturbances of metabolism which frequently accompany the presence of malignant tumors are commonly referred to as cachexia. These may include emaciation, loss of strength, anemia, digestive disturbances, acid intoxication and other manifestations. In many cases, the disturbances of general metabolism may be referred to some direct action of

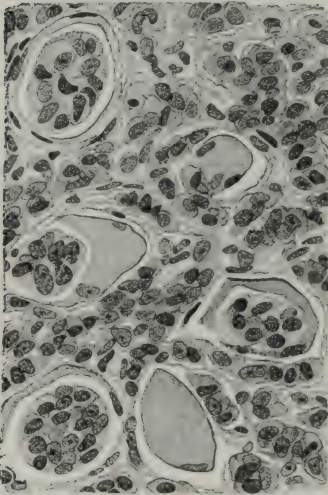


Fig. 143—Invasion of voluntary muscle by cancer, metastasizing from a cancer of the breast.

the tumor itself. For example, cancer of the pylorus may cause obstruction, and thus lead to emaciation and anemia. Consequent to the anemia a variety of additional symptoms may appear. Ulcerated tumors may lead to anemia because of actual loss of blood from the eroded surface. Faults in absorption of alimentary products may occur because of extensive invasion of the liver by tumors, or by obstruction to the thoracic duct. The presence of cancer of the stomach not infrequently is accompanied by deficient secretion of hydrochloric acid and an inability to digest food in the stomach. There are, however, certain cases in which the symptoms of cachexia appear and apparently are not directly referable to the local manifestations of tumor growth. In certain of these cases there is little doubt that psychic disturbances resulting

from knowledge of presence of the tumor may result in loss of appetite, inadequate exercise, and sufficient general disturbance to result in the cachetic manifestations. The question then remains as to whether or not tumors can, in the course of their growth, produce toxic substances which interfere with general metabolism. It can be stated with little hesitation that no such substance has as yet been isolated. As has been mentioned, there is no reason for believing that there are special ferments present in tumors which can have any decided action upon the body. The necrosis of tumors leads to the same products as tissue destruction elsewhere. The free circulation permits absorption of these split protein products so that remote effect may occur. Certainly, fever, anemia and related conditions may occur, but unless the absorption be continuous, prolonged effects are not likely to be observed. The latter condition might be met where metastasis is rich and necrosis frequent and widespread. It is true that in certain tumor cases, fever and leucocytosis are observed, but these conditions are by no means constant, and the most marked cachexia may be entirely

afebrile. Chambers found no important alteration of hydrogen ion concentration of the blood in human cancer cases. There is in human cancer cases, in some instances, a loss of protein and a marked increase in protein metabolism. As Ordway and Morris have pointed out, the same is true in tumor bearing rats in which the output of uric acid and creatine is increased. These facts, as well as others, lead to the belief that there probably is, in certain instances of tumor growth, a distinct alteration of general bodily metabolism. This may result in the manifestations of cachexia, but it must be pointed out that there is little well established ground for believing that this phenomenon is general. In conclusion, most of the cases of cachexia are to be referred rather to the

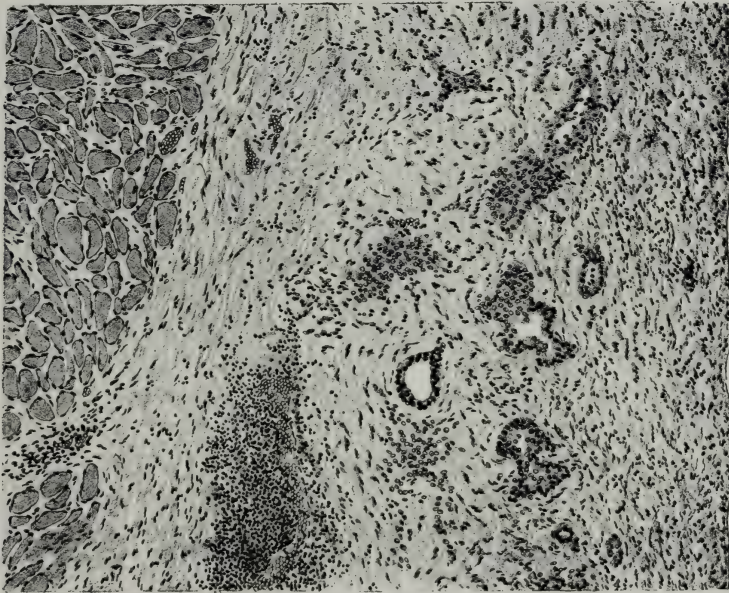


Fig. 144—Subcutaneous implantation of adenocarcinoma following operation, probably due to the transfer of tumor cells during operation.

indirect influences of the tumor growth than to any definite absorbable toxic products of tumors.

Pathological Diagnosis of Malignant Tumors.—The special features of malignancy have been presented. The most important from the point of view of pathological diagnosis are invasive growth and metastasis. The cancer must be regarded as an epithelial tumor, which shows in its histological characters distinct aberration from the normal growth of epithelium. The sarcoma is a connective tissue tumor which, in the arrangement, type of cells and in vascularization, presents certain peculiarities. The more marked the anaplasia, the more certain becomes the diagnosis of malignancy. Aside from the morphological characters of the cell itself, mitotic figures in considerable number are to be regarded as concrete evidence of anaplasia. The absence of complete encapsulation is of great importance. Clinically, the age and sex of the patient, the situation of the tumor, rapidity of growth, invasiveness, as indi-

cated by adhesions to surrounding organs, metastasis either to regional lymph nodes or to more distant points and cachexia are of importance. Certain types of digestive disturbances, blood in vomitus, blood in stools, and other special features may be indicative of malignant growth in the gastro-intestinal canal. Ulceration and hemorrhage are distinctly more common in malignant than in benign growths. The final diagnosis must be regarded as the result of consultation between the clinician and the pathologist. The latter adds to the symptom complex, as observed by the clinician, certain physical characters which are observed in the gross and microscopical examination of the tumor. The final judgment must therefore be a collection and evaluation of all the data available. Often, however, the particular features presented by the pathological examination of the tumor are so manifest and striking that they outweigh, in the evaluation of evidence, any facts which may come from clinical observation.

It has long been recognized that malignant tumors vary in degree of malignancy, as measured especially by invasiveness, metastasis and death. Histologically, tumors of the same organ and of the same type may represent differences as regards anaplasia and differentiation of the cells. This principle was reënnunciated by MacCarty and applied successfully to cancers of the lip and of the skin by Broders, to cancer of the cervix uteri by Martszloff and of the fundus by Mahle, and to cancers of the breast by Greenough. Cancers which show much anaplasia are almost uniformly fatal; those which are highly differentiated, when properly treated, do not recur in a high percentage of cases, and skillful examiners can determine intermediate grades.

Experimental Investigation of Tumors.—The application of experimental methods to the study of tumors has been directed partly toward elucidating the cause of tumors and largely toward examination of the phenomena of transplantation of tumors. Nothing more than a brief indication of the type of work and the results obtained can be presented here. In doing so, we follow in outline the admirable presentation of this subject by Woglom. Although the work to date has not yet resulted in the discovery of the cause of tumors, much valuable information has been acquired in reference to the biology of tumor growth.

Attempts to Produce Tumors.—Experiments of this sort have been directed toward the production of tumor growth by the injection of animal cells, with or without previous experimental preparation of the animal, by treatment of tissues by chemical and physical substances and by the use of supposed etiological agents. It may be said very briefly that the transplantation of adult cells into the same animal or other animals has not as yet led to the production of definite tumors. Cells may live and may grow to form cyst-like masses which sometimes persist for a long time. The transplantation of embryonic tissues and cells results, in certain instances, in the production of cell masses or tissue masses which have certain resemblances to tumors. The most satisfactory of the embryonic tissues is cartilage, which after transplantation may grow considerably. It has not been possible, however, to produce tumors

which exhibit malignant characters by such inoculations, and it is reasonable to regard the growth of such transplant rather as tissue cultures growing under favorable conditions than actual tumor formation. These transplants are likely to be absorbed after a lapse of time. The transplantations of portions of embryo may lead to growth, and a certain amount of differentiation occurs, but finally complete absorption takes place. The influence of pregnancy upon growth of transplanted embryonic tissue has led to divergent results, but the studies of Rous indicate that such transplants grow better in puerperal animals than in either pregnant or non-pregnant animals. Attempts have been made to prepare the field of inoculation by the use of various materials. For example, embryonic tissue has been implanted in association with tumor tissue from other animals without augmenting the growth of the latter. The addition of various dyes such as Sudan III and Scharlach R to tumor transplants has not altered their growth. On the other hand, the injection of kaolin, together with, or before the injection of a filtrate from the Rous chicken sarcoma favors growth of the tumor. The studies of Loeb indicate that some conditions exist within the body which favor or retard tumor growth. By incision of the horn of the uterus of the guinea pig and eversion of the mucous membrane, at a certain stage in pregnancy, small tumor-like masses were produced, referred to as deciduomata. Loeb formulated the hypothesis that there is secreted from the corpus luteum a substance which so sensitizes the mucous membrane, that when the incision releases pressure or tension upon the epithelium, tumor-like growth occurs. There is thus an interaction of two factors in the production of this type of growth.

Irritation as a possible cause for cancer has long been considered and was proposed as a definite hypothesis by Virchow (Alter). Examples are numerous and include cancers arising from chronic ulcers and sinuses (Knox), scrotal cancer of chimney sweeps and cancer upon the abdomen of the Kashmir natives who wear Kangri baskets. Numerous other instances support the belief that chronic irritation is of great importance. Just how the x-ray produces cancer is not known, although there is evidence that x-ray in proper doses may stimulate tissue and lead to proliferation. Although the cancers in x-ray workers have followed the production of burns, nevertheless, burns are not a necessary precursor to the development of such tumor growth. Experimental work with chronic irritation leaves no doubt that tumors may follow such a mechanism. For example, the repeated scraping of the rabbit's lip has led to the development of papillomatous tumors. Of great importance is the recent work in the production of tumors by the use of tar and its products. Yamagiwa was able to produce both epithelial proliferation and penetration of deeper tissues by the cells, as the result of painting the tar upon the skin surface of the rabbit's ear, and to produce less typical cancers by the injection of tar, except in one instance where he produced a sarcoma. Fibiger then found that mice which are naturally more susceptible to tumor growth responded more constantly to this form of irritation. Bloch and Dreifuss, by using a distillate of tar which comes off at 300° C., were able to produce malignant

tumors in white mice in practically all instances. That this influence is purely the result of chronic inflammation is yet to be proven, and will be discussed further in connection with Scharlach R tumors. Following the observations of Reinke that the injection of ether into the eye of the salamander produces a typical epithelial growth, B. Fischer and various others have studied the influence of lipid solvents. By the injection of olive oil and Scharlach R under the skin of a rabbit's ear, the injection being made under pressure, there follows proliferation of epithelium, which, although not progressive and tending to disappear after all the oil is absorbed, nevertheless, resembles closely an epidermoid cancer. Under similar experimental conditions, this observation has been confirmed many times. Fischer believes that the dye contains a chemotactic substance, which he calls attraxin, capable of stimulating the epithelial growth. Helmholtz, however, expressed the belief that there are substances in the dye which combine with the tissue so as to permit of more ready proliferation of the epithelium. Since J. Loeb came to the conclusion that artificial parthenogenesis depends upon some fat or lipid solvent, it was thought that the mixture of oil and dye operates in this fashion to produce epithelial cell division and proliferation. Bullock and Rohdenburg, although they agree that these substances stimulate epithelial proliferation, found that all lipid solvents do not act to produce tumors in the same way as does olive oil, and therefore, came to the conclusion that the application of Loeb's observations is not justified in this instance. Of considerable interest is the fact that the injection of ether in embryonic tissues leads to a greater growth of embryonic tissues in transplants than if no ether be employed. It must be considered that certain lipid solvents may produce moderate stimulation not exceeding normal growth, and that others may lead to malignant proliferation.

The attempts to associate with tumor growth causative organisms, either vegetable or animal in nature, have been extremely numerous. Many of the supposed parasites have been shown to be degeneration products of the tumor growth itself. Others apparently are the result of contamination of tumors by bacteria of various kinds. The establishment of a very definite etiological relationship is extremely difficult, for ultimately there remains the question as to whether the production of tumor depends upon chronic inflammation induced by the parasite, or upon direct stimulating properties of the parasite. Common warts are looked upon as a variety of tumor growth, and Wile and Kingery have been able to produce them by filtrates from warts. Kingery has been able to do this through the second generation. Somewhat similar, but not identical, has been the work of Rous with the chicken sarcoma which he has described very carefully. This can be transplanted by means of a filtrate, if kaolin be injected with the filtrate. In this instance, it apparently is necessary that the soil be prepared before the tumor will grow. There is no doubt that the chicken sarcoma of Rous shows all the histological characters of a true tumor. In spite of this, certain authorities are inclined to regard the growth as of granulomatous character (Tendeloo). Gye and also Barnard have used this tumor in investigating the cause of tumors. Filtrates of it contain ultramicro-

scopic spheroids which are believed to be microorganisms. As a result of their experiments, Gye believes this to be an extrinsic factor common in the cause of various tumors, which operates with another special intrinsic cause for each type of tumor. The intrinsic factor may possibly be the archusia of Burrows, to be referred to subsequently.

Of great importance are the investigations of Fibiger who has been able to produce carcinoma in the stomach of the rat, by feeding them cockroaches infected with a nematode worm which he named the *spiroptera neoplastica*. The tumors occurred in twelve out of sixty-two rats so fed and pulmonary metastases were observed in two instances. Apparently the first result is a chronic inflammation followed by a profuse growth of papillary tumors. These infiltrate through the stomach wall and show metaplasia of the epithelium with keratin production. Subacute inflammation persists in the tissues between the tumor growth, particularly in the form of infiltration of eosinophile leucocytes. No worms or ova are found in the metastases, although the original stomach tumors commonly show the parasites. There is here no question of preparing the field for the operation of the parasite, nor of constitutional alteration on the part of the animal. Although it appears probable that the fundamental change in the stomach is a chronic inflammation, it cannot as yet be said whether or not products of the parasites have a specific stimulating influence upon the animal cells. E. F. Smith has published extensive studies of crown gall of plants. This process is supposed to be of essentially the same nature as tumors of animals, and he has isolated an organism, the *bacillus tumefaciens*, which is capable of producing these growths. Levin and Levine, however, conclude that the *bacillus* produces primarily an inflammatory reaction which subsequently becomes tumor-like, not because of the action of the organism, but because of some intricate mechanism within the host. Tumor growth is undoubtedly associated with parasites of a variety of kinds, but practically all the evidence so far submitted, with the exception of the common wart and that of the Rous chicken sarcoma, indicates that the connection with parasites so far demonstrated has been very largely that of the production of chronic inflammation, which so alters the proliferative capacity of various cells that tumors may develop.

Transplantation of Tumors.—Although several investigators have succeeded in transplanting tumors from one animal to another of the same species, the first systematic study was that made by Moreau in 1891. Ten years elapsed before the present widespread interest in the subject was awakened by the work of L. Loeb in this country, and of Jensen in Denmark. The former, working with a rat tumor, and the latter, with a mouse tumor, were able to transplant through many generations. Both decided that the new growth was a multiplication of the transplanted cells, but Loeb was of the opinion that the experiment did not absolutely exclude the possibility of transplantation of parasites at the same time. This work was the starting point of a vast number of studies, which since then have been conducted. It is impossible to say how far this work may be carried in the future, but the results to date have not

disclosed the cause of tumors. Nevertheless, much valuable information has been collected on the general biology of tumor growth, the conditions of transplantation, the reaction on the part of the host, natural and acquired resistance and allergic states. The larger questions of etiology and therapy have not yet been solved.

Most of the studies have been made, as has been stated, on tumors within a given species. Attempts have been made to transfer from one species to another, and although certain successful experiments have been conducted, such attempts have been generally unsuccessful.

When tumor masses are transplanted into a new host, many of the cells show necrosis and others survive. In the larger grafts the central masses die and the peripheral cell masses retain life and proliferative capacity. Much attention has been given to the reaction on the part of the stroma of the host. Apparently, the essential cells of the tumor are the main ones to survive, and the blood vessels and connective tissue undergo hyalinization and final disappearance. The connective tissues of the host react so as to form what is essentially granulation tissue, with new blood vessels and fibroblasts. These penetrate along the lines of the original connective tissue of the tumor graft, and ultimately replace this so as to furnish a new stroma for the growing tumor. This reaction is specific in character, since as the tumor grows, the original tumor type of supporting framework is maintained throughout. There are, however, certain variations in the vascular content of the new supporting framework. In some instances, this new tissue is richly vascularized and the reaction is spoken of as angioplastic. In other instances, where the vascularization is poor the reaction is referred to as fibroplastic. In instances where angioplastic reaction is observed necrosis is not marked in the tumor, whereas in the reverse condition, necrosis may be frequent and widespread. It has been noted repeatedly that when a primary tumor of an animal is transplanted into a series of other animals, the number of animals in which the grafts grow is relatively small, but as succeeding generations of transplants are made, the rate of success increases and, in certain instances may attain 100 per cent. Ehrlich and certain other investigators regard this as indicating that the tumor increases in virulence through successive generations. This is attributed to an increased resistance on the part of the tumor cells against the destructive forces of the host, and is comparable to similar processes exhibited by bacteria and by trypanosomes. Bashford and his colleagues consider, quite advisedly, that this use of the term virulence, a term which even primarily is not very clear, is not justified in reference to tumor cells unless its use be qualified in many ways. Bashford, therefore, prefers the term "adaptation" and considers that during the successive generations, the tumor cells adapt themselves to the new conditions which they find in the hosts. With this adaptation comes an increase in growth energy, which, however, is not continuously on the increase but shows waves of diminution. Clowes and Baeslack found that exposure of the grafts to certain chemicals, and for short periods to temperatures of about 40° C., increase the growth energy, but Ehrlich was unable to confirm this. It is, however, in

accord with other observations of the growth of cells. That such factors play a part in the transplantation into animals remains open to doubt. The success or failure of transplantation depends upon a number of factors. When bacteria are inoculated into animals the results are fairly uniform, but in the case of tumor transplants, succeeding growth may or may not occur. This suggests the possibility that the soil for growth provided by the individual animal varies considerably. Although Loeb was of the opinion that the soil influenced to a considerable degree the success of transplantation, the work of Bashford, Murray and Cramer gave somewhat different results, and they were inclined to attribute little significance to the soil in successful transplantation. Nevertheless, results are improved by having animals of fairly uniform character, particularly as regards race and age. Success also varies somewhat with the situation of inoculation, and comparative studies are best conducted when some uniform standard of inoculation is employed. Although the growth of the inoculated tumor may be delayed over several months, yet as a rule the tumor becomes apparent in about the second or third week after the inoculation.

Success varies also with the material injected. Certain tumors can be transplanted only with greater difficulty than is true of others. Since growth energy follows a somewhat irregular curve, the best chance of success is likely to follow inoculation at a period when growth energy is at a high point. Nevertheless, stationary or receding tumors may be transplanted, but it is generally found that their growth energy is reduced. This is believed to be due to a change in the essential cells of the tumor. Metastatic nodules can be successfully transplanted, but it is difficult to state whether these show the same ratio of success as the original tumors. The inoculation of mixtures of two types of tumor, have in certain instances been followed by the production of mixed tumors. This, however, varies with the type of animal, and it has been shown that a mixture inoculated into two strains of mice may lead to the development of one tumor in one strain and another tumor in the other strain. Thus, it appears that in order to develop a mixed tumor, the biological conditions for growth of each component must be approximately equal.

Difficulties arise in the transplantation, which are sometimes not easily controlled. For example, tumors which grow well in animals of one country may fail to grow in animals of other countries. Certain tumors, at least upon first transplantation, must be inoculated into animals sometimes of the same strain and sometimes even of the same brood. Numerous studies have been conducted in regard to diet as a factor in tumor growth. Thus, a carbohydrate free diet has been found to limit the number of successful transplants, but this is not true for all tumors. A simple restriction in the amount of food has limited growth of tumors, but again this is not constant. The substitution of lime for other salts in the diet has been found to retard the success of transplantation, but if a take be secured, its growth will be hastened by restoration of the original diet. Transplantation and growth are favored by the injection of cholesterol subcutaneously and the same is true of the use of tethelin. Castration and also splenectomy have favored experimental inoculation.

Spontaneous regression and cure of implanted tumors may occur, as is true of non-experimental tumors. As has been pointed out, the transplants from regressive tumors exhibit reduced growth energy. The regression may be initiated by necrosis and degenerative changes in the tumor, which are reacted to by the surrounding stroma in the same manner as to other forms of necrosis. Granulation, fibrosis and phagocytosis and absorption of fluid necrotic material take place. Apparently, in some tumors the process is largely in the form of a progressive fibrosis, which leads to atrophy and disappearance of the tumor. Woglom found no distinguishing features in the essential cells of the tumors, to indicate regression.

The study of human tumors shows that at different periods they may show certain variations in histological characters. For example, in glandular tumors the acini, at different periods, vary in size, shape, papilla formation and multiplicity of lining layers. During the course of cultivation of transplanted tumors similar changes are commonly observed, although the tumors retain their general original structures through many generations. One of the most important, and probably the least understood change is that of carcinoma into sarcoma, after several generations of transplantation have occurred. This may be rather sudden so that the sarcoma appears rapidly and no trace of the original carcinoma may be found. It is improbable that the original tumor was mixed and, that owing to changes in the field of growth, the original sarcoma outgrows the carcinoma. It is conceivable, however, that the growth of the epithelial cells may have a desmoplastic influence upon the stroma so that the latter takes on a sarcomatous type of growth. Even this does not explain the disappearance of the epithelial tumor, unless it be supposed that the sarcoma arises at a period when the growth energy of the epithelial element is in a state of retrogression. Ewing suggests, on good grounds, that probably in many instances the spindle cell forms, occurring in the sarcomatous type of growth, are not truly connective tissue cells but represent false metaplasia of epithelial cells.

The cells of tumors have been cultivated after the same technique used in the cultivation of other living mamalian cells. It is practically impossible to measure growth energy with any degree of accuracy by these methods, but it is of importance to note that tumor cells grow with practically equal facility in plasma derived from the same animal, from immune animals of the same species and with perhaps a less degree of readiness in the plasma of animals of other species. It would therefore appear that animal plasma has no important inhibitory effect upon cell growth, as an expression of immunity or resistance to tumor implantation.

Resistance.—The term resistance is applied here rather than the term immunity, because of a broader significance of the former and the failure to demonstrate the specificity demanded of the latter. Tumors may arise non-experimentally in animals which have been resistant to inoculated tumors, and thus no immunity against tumors as a group can be considered to exist in this instance. Resistance to tumor implantation may be either natural or acquired.

Natural resistance may be considered in reference to age, race, health and the presence of pregnancy. Since most non-experimental tumors arise in advanced life, it is to be expected that transplantation could be accomplished best in the later periods of life. This, however, has been found untrue, and a greater percentage of success is obtained when young animals are employed. Thus, although age apparently offers conditions favorable for the inception of a tumor, it does not offer excellent conditions for the implantation of a tumor already established in another animal. The conditions, which control the origin of a tumor, must therefore be different from those which render it suitable for transplantation. There is little doubt that transplantation within the same race of animals is more successful than in different races, and that species offers a barrier which is surmounted only with great difficulty. As general ill-health interferes with the success of transplantation, we find a parallel with the interference exhibited in poor nutrition. Experiments so far have failed to show any important difference between the sexes as to availability for transplantation. Although certain investigators have found that pregnancy offers a condition unfavorable to transplantation, others have denied this. The weight of evidence seems to favor the former view. It has been suggested that the differences are due to the fact that embryos require much the same type of nutrition as do growing tumors, and that if a considerable number of embryos be present, the chance of successful transplantation is less than if only a small number of embryos be present.

Numerous studies have been made concerning actively and passively acquired resistance to tumors. Following the observation of Clowes and Baeslack, that animals which have recovered from inoculated tumors are refractory to subsequent inoculation, extensive studies have been made concerning this phenomenon. Although there has been some question as to whether or not this represents a separation or isolation of animals, more or less immune, from those which are susceptible, nevertheless, the general opinion now is that the resistance is due to the former tumor implantation and must be regarded, therefore, as an active resistance. Upon investigation of the problem as to whether or not this resistance is strictly specific, it is found that although the resistance to the same tumor is somewhat greater than to other tumors, yet the phenomenon can be regarded in a general way as universal. Ehrlich applied the term "pan-immunity" to express the process. There followed a series of experiments, in which attempts were made to immunize the animals or excite resistance by the injection of tumor cells killed by chemical or other methods. Such vaccination was not successful, and it was concluded that in order to establish the resistance the actual growth of tumor cells is necessary. It was then found that normal cells from the same species operate in essentially the same way as the implantation of tumors, and prevent successful subsequent inoculation. Vaccination with the animal's own tissues was unsuccessful, but killed normal cells operated in the same way as killed tumor cells. Vaccination has failed to influence the growth of non-experimental tumors in animals, and the attempted vaccination treatment of human tumors has been equally unsuccessful. Injection of the

blood serum or plasma of animals which had acquired active resistance, or of animals which had been immunized to normal cells, is ineffective, and it can be stated very definitely that passive resistance cannot be conferred. The factor of resistance is not contained within the body fluids. Ehrlich proposed his theory of athrepsia, which supposes that in the resistant animals there is an absence or decrease in a certain substance which specifically stimulates the nutritive capacities of the tumor cells, but there is little experimental evidence to support this. It may be stated that at the present time no satisfactory hypothesis can be offered to explain the resistance to tumor growth. Wood points out that no evidence has been collected to show that spontaneous regression of human or primary animal tumors is due to immunity.

The study of the local reactions to tumor implantation throws some light on the process but does not completely explain it. In resistant animals the implantation is followed not by a production of stroma, as in successful tumor grafts, but instead leads to an inflammatory reaction with the appearance of leucocytes, plasma cells and large numbers of actively phagocytic endothelial cells. Van Dungern and Coca offer the hypothesis that the presence of the previous tumor, subsequently absorbed, produces an allergic state in the animal, which so alters the reactive capacity that instead of furnishing stroma, destructive forces are set to work. The presence of large numbers of lymphocytes about the inoculated tumors and also about human malignant tumors, make it seem probable that these cells offer some special resistance to tumor growth (see MacCarty and Kehrer). Immunity cannot readily be induced in splenectomized animals, and Murphy has found that the chick embryo will not resist implantation of tumors, until the spleen and lymphocytes have appeared. Murphy and his collaborators reduced the lymphoid tissue and circulating lymphocytes by employing the x-ray, and found that there was a decreased resistance to tumor implantation. Increasing the number of lymphocytes by the use of dry heat on the animal, they demonstrated a high degree of immunity to certain transplantable tumors in mice. Although Wood and his collaborators have been unable to confirm the studies of Murphy, yet on the other hand, Russ, Mottram and others have had essentially the same results as has Murphy. Thus, it seems probable that the lymphocytes play an important part in the resistance to tumor growth.

The study of immune phenomena *in vitro* is rendered difficult because of the practical impossibility of securing tumor material free from tissue juices or blood of the host. Attempts to establish clinical tests on the basis of precipitins, complement fixation, the meiostagmin reaction of Ascoli, and by the method of anaphylaxis have been unsuccessful. This may be due to the technical difficulties, but probably is due in large part to a lack of cellular specificity within the species.

Theories as to the Origin of Tumors.—The cause of tumors is not known. There are, however, certain factors which appear to operate as predisposing causes, and in addition a considerable number of hypotheses concerning the nature and origin of tumor growth. It is impossible to separate these two

phases of the subject, and it is considered desirable to present first the theories concerning origin of tumors before discussing what may be referred to more directly as causative agents. There is necessarily, however, a certain amount of overlapping of these two phases of the subject. From a hypothetical point of view tumors may arise from external or exogenous causes, or from endogenous causes. Those theories concerned with exogenous origin are particularly the theory of irritation and the theory of parasitic cause of cancer.

Irritation.—Irritation may be of traumatic or various other origins. Traumatic irritation may result from direct momentary trauma, or be the result of some process which leads to continuous or frequently repeated insults. The history of trauma preceding the development of certain tumors may be either simply coincidence or have some direct bearing on their origin. Thus, in a large series of glioma of the brain more than 8 per cent. of the cases showed a history of trauma (Ewing). Such a history is commonly obtained in tumors of the breast, certain tumors of the bone and of the testicle. It is sometimes recorded in cases of benign tumors, such as fibroma. Prolonged irritation either in the form of repeated insults to the tissue or in the form of chronic inflammatory processes of one variety or another is common, particularly in reference to epithelial tumors. Habitual irritation, as in cancer of the lip of smokers, cancer of the abdominal wall in the wearers of the Kangri baskets and cancer of the mouth in betelnut chewers, are familiar examples of cancer from irritation. Chronic inflammation may be produced in the mouth by jagged teeth; in the skin by chronic diseases, particularly chronic eczema; in the mucous membranes and skin by chronic ulcers; and in the deeper tissues by persistent sinuses. Cancer of the esophagus is most common at the narrow parts and cancer of the stomach at the pylorus, suggesting that cancers of these organs arise where repeated insult is most likely to occur. Cancer of the gall bladder and of the renal pelvis is commonly associated with calculi. Of the specific granulomata, syphilitic psoriasis of the tongue, syphilitic lesions of bones, and tuberculosis of the skin in the form of lupus, may be followed by tumor formation. Occupation may have an important bearing on the origin of tumors. It is well known that inadequately protected x-ray workers may develop cancer. Cancer is found also among paraffin workers and workers in anilin dyes (Hamilton), and is reported in the form of cancer of the lung among workers in dusts of various kinds (Uhlig). From clinical and pathological observations, such as those indicated above, there seems little doubt that chronic irritation plays some part in the development of tumors. In interpreting the origin of tumors following momentary trauma or inflammation of short duration, there is always the possibility that the tumor may have existed before the injury, or that a precancerous condition may have existed which was stimulated to growth by the injury, or that embryologically misplaced organs or cell groups, possibly more susceptible to stimulation to growth than normal cells, are thrown into activity by the injury. Experimental evidence leaves little doubt that normal cells cannot develop tumor growth. On the other hand, certain influences may so disturb normal cell relations as to lead

to tumor growth. This may be the result of some direct stimulus operating upon the cells to produce increased cell division. The same factors may lead to a disturbance of balance in which certain cell groups go on to active proliferation because of loss of restrictive influence on the part of surrounding cells. It is also possible that certain cell groups are separated off from the major mass in the course of chronic inflammation, and by virtue of isolation or crowding are qualified to go on to indefinite proliferation. There can be no doubt that chronic inflammation may lead to a condition which finally results in tumor formation. This does not solve the problem, however, since many



FIG. 145—Calculi in gall bladder, with carcinoma of gall bladder directly invading the neighboring liver.

tumors show no history of trauma or chronic inflammation. Nevertheless, chronic irritations of various sorts represent preventable conditions and, as Coplin has emphasized, these observations form a very important basis for methods of prevention of tumors, particularly cancer. The importance of irritation is borne out by experiments which have been quoted above, as for example, the prolonged scraping of the lip of the rabbit and particularly by the so-called tar cancers.

Parasites.—The tumor cells themselves lead a sort of a parasitic existence in the host, but all studies so far conducted leave no doubt that these cells are part of the animal itself and are not introduced from without. Parasites introduced from without may have some influence in the development of tumors.

This, however, is indirect and more particularly operates through chronic irritation or chronic inflammation. Thus, as has been mentioned, tumors may rarely develop on the basis of tuberculosis or of syphilis. Tumors may occur in connection with diseases due to higher vegetable parasites such as blastomycosis, and are observed in diseases due to the higher animal parasites such as bilharziasis. All these diseases, however, show a very small percentage incidence of tumor formation and there is no real suspicion that the parasites concerned have to do with the production of tumors. Certain arguments have been propounded, supposedly in favor of the infectious origin of tumors. Cancer houses and cancer streets have been reported in the older literature, but more careful examination with modern epidemiological methods shows no basis for support of this hypothesis. Tumors do not occur in epidemic form and in the observations of tumors among lower animals, particularly mice, no evidence can be presented for cage infection or epidemics of any kind. Much time has been spent in studying supposed parasitic inclusions in tumor cells. The Russell fuchsin body has been shown to be simply a form of hyaline degeneration of the cells. The "bird's eye" inclusion showing a deeply stained central body with a surrounding areola is chiefly the result of secretory processes. Bacteria, such as the micrococcus neoformans and higher vegetable organisms such as the saccharomyces neoformans, various protozoa and higher forms of animal parasites, including various forms of nematodes and the tenia crassicolis, have been studied extensively. The work of Fibiger with the *spiroptera neoplastica* has been referred to above, and since neither these parasites nor their ova can be found in the metastases from the stomach tumor, it is reasonable to suppose that chronic inflammation is at the base of the cancer production. The action of parasites is variously supposed to be a direct and certain cause of cancer either as a result of symbiosis between parasites and cells (see Gye), or the result of transfer of parasitic soluble substances, perhaps toxic in nature, from the parasite to the animal cell. In spite of modern work with bacteria in tumors, such as for example that of Nuzum, it may be stated with little hesitation that a direct specific parasitic cause of tumors has not been demonstrated (Kross).

Theories as to Endogenous Causes.—The examination of supposed exogenous causes leaves practically nothing of importance in that connection, except that certain types of tumors may originate on the basis of chronic irritation and perhaps of trauma. The cause of tumors therefore must reside at least to some degree within the organism itself. This has led to the development of a large variety of theories, the most important of which are outlined in the following paragraphs.

Embryonal Theory.—Although other investigators have suggested the same general theory, nevertheless, to Cohnheim is ascribed the enunciation or clarification of the proposition that tumors arise as the result of misplacement of tissues and cells during embryonic life, and that subsequently these misplaced tissues proliferate unrestrained by ordinary laws of growth. This presupposes that the embryonal cell retains its capacity for unlimited

proliferation, and further indicates that actual physical misplacement is not necessary; but if the embryonic capacity for proliferation remains, tumor growth may result. From both points of view it is necessary to suppose that the cells retain great capacity for proliferation. There are certain types of growth usually classified as tumors which reduplicate in greater or lesser part the embryonic cell layers. These are the teratomas. Somewhat similar is double or parasitic monster formation. The border line between monsters and teratomatous tumors is very difficult to draw, and some authors regard teratomas rather as a variety of monster formation than of true tumor growth. The teratomas, however, grow within the host, are parasitic in character, derive their nutrition from the host and in certain instances show unlimited growth capacity. It is for these reasons that the teratomas continue to be regarded as tumors. The fact that malignant tumors may originate on the basis of teratoma has no place in arguments for or against regarding teratomas as tumors. The arguments in favor of the embryonal theory of Cohnheim are numerous. Certain tumors appear at birth, particularly the teratomas, but other types of tumor may occur including such malignant tumor as the carcinoma. Similar teratoid tumors occur after birth and may be observed well on into puberty or later life. These have essentially the same characters as the congenital tumors and are regarded as identical. They exhibit tissue which closely resembles one or more layers of embryonic structure, and there is no reason for not believing that these originate in misplaced or misdirected embryonal cells. The fact that tumor growth is not uncommon at points where ectoderm meets entoderm, as for example, in the margin of the anus, or the junction of the esophagus and stomach, makes it possible that cells misplaced during fusion subsequently undergo cancer or malignant tumor growth. The same is true regarding points of obliteration of embryonic structures such as the notochord, and points of obliteration and cell migration as in the branchial clefts. Tumors not uncommonly arise from accessory structures such as supernumerary breasts, accessory pancreas, accessory adrenals, accessory thyroid or parathyroid, and it seems possible that the malformation which leads to these structures may also leave some remnants with embryonic characters, which produce tumor growth. It is well known that certain cell remnants are frequently included in the mature organism. The best example is the remnant of adrenal frequently found in the kidney, and in fact in almost any situation in the urogenital tract. These not uncommonly undergo tumor formation. The choristoma and hamartoma have been discussed above. Against this theory is the fact that certainly all tumors do not originate in this fashion; for example, cancer of the skin can sometimes be seen originating in proliferating epithelium, which cannot in any way be identified as embryonic in type. The fact that in nucleocytoplasmic ratio (Sokoloff) and in other characters, the tumor cells may closely resemble embryonic cells does not mean that they are identical. The normal embryonic cell proliferates and gives rise to normal adult cells, and the mere misplacement of certain cells or groups of cells gives no adequate reason for their proliferation to form tumor

masses. In normal development, growth energy appears to decrease as differentiation proceeds and maturity is reached, and there is nothing in the Cohnheim theory to explain why this growth energy remains persistent over many cell generations. It may therefore be said in summary that although the Cohnheim theory explains the origin of a certain number of tumors, more particularly the teratoid tumors, there are numerous other tumors which cannot be explained on this basis. The experimental implantation of embryonic tissues into animals does not commonly lead to tumor formation, and it is therefore necessary to explain actual tumor growth on some other basis. Fundamentally, then, the problem concerns itself particularly with explaining why cell growth becomes autonomous, that is self-dependent and not limited by the laws of normal growth and differentiation.

Theories of the Nature of Cell Autonomy.—Numerous theories have been offered to explain the nature of the change occurring in cells, by which they begin and continue the unlimited proliferation of tumor growth. It is only possible here to indicate the outlines of some of these hypotheses. They are by no means completely satisfying, and although they point out certain changes which occur, they do not explain why these changes occur. As general biology becomes more extensively applied to the problem, the hypotheses must be clarified, but it seems probable that final solution rests upon determination of the fundamental nature of life, growth, reproduction, senescence and death. It cannot be said with certainty that even excluding parasitic causes of tumors, all extracellular stimulation of cell growth is excluded, and conversely it cannot be said that the origin must necessarily be intracellular. The influence of hormones and other internal secretions certainly plays a part in the appearance of senescent and fibrotic changes in various organs, but this cannot be directly applied to tumor growth. Beard has offered the hypothesis that the external secretion of the pancreas limits cell growth, and that its suppression removes this inhibiting influence; there are, however, no good grounds for accepting this view. As to other factors, which may influence cell growth from without, little of importance as regards tumors is known other than the statements made under the heading of exogenous origin. The important remaining hypotheses concern the relation of cell to cell, internal changes in cell character and hereditary influences.

Theories of Cell Relations.—Probably the most outstanding of these theories is that which deals with *tissue tension*. It is well known that tumors show their highest incidence in advanced life. This is common to all animals. Remak and Thiersch pointed out that the outstanding element in embryonic development is the growth of epithelium, which appears to be limited especially by the growth of connective tissues. Thiersch supposed that in advanced life, deterioration of connective tissues removes the restraint upon other cells and permits the beginning of unlimited growth. This he referred to a release of mechanical pressure, and the idea is supported by L. Loeb's experimental work on deciduomata and by his observation of renewed growth following incision of the capsule of tumors. Waldeyer was of the opinion that the epi-

thelial elements lose their vigor and that the surrounding connective tissue proliferates so as to isolate cell masses. The epithelial cells then become necrotic as a rule, but may form cysts or in certain cases, following changes in the connective tissue resembling inflammation, the epithelium may exhibit malignant proliferation. That senile changes are limited to the connective tissue as hypothesized by Thiersch is not true; other cells are involved in the process and cannot be considered as normal. The hypothesis leaves unsettled the question as to whether the non-connective tissue cells simply exhibit normal growth or increased growth. Waldeyer's hypothesis offers no reason for the multiplication of isolated cell groups. Ribbert believes that there are no real increases in growth energy and Weigert and Roux maintain that the regenerative capacity of cells is practically constant and cannot be increased. Lubarsch found this conception incompatible with the marked proliferation in metastatic foci, where enormous and rapidly growing tumors occur. Ewing differentiates between those regenerative properties of cells which lead to healing and repair, which are practically constant, and the "mere power of multiplication without organization" or reparative function, exhibited in tumors. He states that "tumor cells seem to have more than their ancestral power of growth as when without pressure they erode bone."

It is further possible that alterations in supply of nutrition may favorably influence certain cell groups, either isolated as in the Cohnheim theory and in the older Ribbert theory, or in normal relations with or without changes of mechanical pressure, but this point is by no means established. The Ehrlich hypothesis, referred to in the section of experimental work, supposed a special nutrient molecule but not necessarily an increased supply of nutriment.

The process of development and regeneration in animals and plants shows that there is a normal balance maintained under ordinary conditions, but governed by numerous factors of stimulation, nutrition and perhaps of purposive growth. The individual cells grow in well defined relation to the good of the entire organism and are subject to the laws of biological organization. With this conception, it can be understood that the tumor is not subject to the laws of organization (in the biological sense) and is no longer controlled by the welfare of the entire organism. Why the change occurs is not especially clarified by this idea of loss of tissue and cell balance.

Not only may cells be displaced in embryonic growth, but they may be more or less isolated by changes occurring in postnatal life. Thus, in an ulcer, epithelial cells may be isolated in the granulating surface. In chronic fibrosis of various organs, cell groups may be separated from the main group. Ribbert's newer hypothesis is to the effect that all tumors originate in isolated cell groups, but that some further stimulus is necessary to tumor growth. The stimulus may be frequent, as inflammation, but only produces tumors when cell isolation has occurred. This explains why tumors do or do not occur under the same external conditions, but does not coincide with the observations on early tumors, where the growth may be seen originating in cell groups in continuity with the main mass.

Burrows and Johnston have extended the Ribbert hypothesis largely on the basis of investigations of tissue cultures. They support the idea of a driving substance of the cell, archusia, which ordinarily is diffused into the body fluids, but when cells are crowded together may accumulate to induce inordinate multiplication. It is difficult to understand how this occurs in the living body, but Maximow's observation of cancer-like changes in cultures of breast tissue lends support to the hypothesis. Carrel also produced tumor-like growth of cultures of monocytes. When such cultures establish tumor growth, by transplantation to the living body, Burrows' hypothesis will be more firmly established.

Theories of Internal Changes in Cells.—It is impossible to draw a sharp line of distinction between these theories and those that have to do with cell relationships, and this artificial separation is only for purposes of simplification. Tumor cells are different from normal cells in general biological activities and also in certain morphological ways. Complement fixation, meiostagmin reaction and Abderhalden test, although by no means constant and of little clinical value, indicate that there are inherent peculiarities of tumor cells. The fact that tumor cells resist cold and certain chemicals, as well as the conditions of transplantation, better than do normal cells, points toward a state of lesser differentiation on the part of the tumor cells.

Adami, following somewhat the same line of argument as Beneke, supposes that functional activity employs energy that might otherwise be used for growth. Cells so placed that they cannot function but continue to receive nourishment, multiply and assume the "habit of growth." Von Dungern and Werner suggest that through some unequal distribution of biological properties, a strain of cells appears which has lost the usual inhibition of cell growth. Hauser considers that as variation occurs in animals and plants (mutation) with the development of new characters, so the cells within an individual may become separated into strains, which have the capacity for unlimited growth. Somewhat more specific is the idea of Oertel, that as protozoa may have two nuclei, one controlling growth and the other nutrition and function, the chromatin of metazoan cells may contain both elements in different loops. Through some abnormality in mitosis, the cancer cell possesses mainly or solely the chromatin which controls division and multiplication, thus leading to a race of cells with little function and great proliferative capacity. Somewhat similar is the hypothesis of Farmer, Moore and Walker, that tumor cells exhibit the reduction in chromosomes seen in sex cells and the chromosomes assume the arrangement of sex cells (see Boveri). These are not supposed to be sex cells, nor is there any good reason for assuming that such cells are fertilized cells, but they have the great growth energy of sex cells. Warburg points out certain features of the metabolism of cancer cells, resembling that of embryonic cells. This does not explain why they continue as undifferentiated cells instead of proceeding to differentiation and organized growth. Space need not be consumed with discussion of these theories, since they are presented largely as a matter of general interest. Probably much nearer

the truth are the theories which deal with dedifferentiation, a property of tumor cells of fundamental importance.

Dedifferentiation. Anaplasia.—The phenomenon of dedifferentiation (*Entdifferenzierung*) indicates a retrogression of differentiation, which carries with it an increased capacity for independent existence. The most noteworthy of the hypotheses offered upon this basis is the von Hansemann theory of anaplasia. He regards the irregular and atypical mitoses of tumor cells as indicative of a cell change whereby races of cells are produced possessing great capacity for multiplication. This is a retrogressive change, not in the ordinary sense of cytoplasmic degeneration, but in a broader biologic sense. The parent cells of the tumor have reached mature development and then have regressed in differentiation. Thus, there may be minor degrees of reversion, such as have been referred to in connection with the endothelial cells in inflammation, or there may be marked reversion to a type of cell whose growth is that of a parasite within the tumor bearing host. As Marchand points out, the cell has not resumed embryonic characters, since embryonic cells tend to differentiate, whereas tumor cells are not only functionally and structurally different but apparently have lost their capacity for differentiation. Marchand supposes that deteriorative changes in the cell result in altered metabolism, and that the products lead to unlimited growth of neighboring cells. Beneke doubts that cells can actually revert in the sense of anaplasia and considers that loss of function and increase in growth power, a condition which he calls *kataplasia*, is the only difference between the normal and the tumor cell. In the more recent discussions of the subject, the presence of atypical mitosis has been thrust into the background as an essential part of the theory of anaplasia, but the idea of essential changes in the nature of the cell is widely accepted.

Bashford laid much stress on the senescence of cells as leading to tumor formation. There is much to support the hypothesis that as cells age, they may under certain experimental conditions, such for example as starvation, exhibit dedifferentiation. Von Hansemann admits that the theory of anaplasia does not explain its origin. Goodpasture, as the result of a study of senescence and tumor formation in dogs, reaches the conclusion that senescence of cells is of the utmost importance in explaining dedifferentiation. Progressive cellular differentiation ultimately results in senescence, which in its turn may lead to alterations of function and structure, perhaps with the accumulation of injurious products of metabolism. Many cells die and the remainder may show no change, or lose specialization. As specialization is lost, capacity for growth and redifferentiation may increase. Lesser degrees of loss of specialization may be restored and regeneration occur. With extreme degrees of dedifferentiation, growth capacity becomes dominant and tumor growth may occur. While no final conclusion can be reached, it seems that the theory of anaplasia represents well the nature of the change occurring in tumor cells, and that the biological nature of senescence of cells accounts for the assumption of independent growth activities of the cell.

Heredity.—Decision as to whether or not heredity plays a part in the

occurrence of tumors remains an unsettled problem. If a parasitic cause for tumors be discovered in the future, it will then remain to be determined whether this can be transmitted in congenital manner, or whether some predisposing cause is heritable. It seems probable that some tumors are heritable at least through predisposition, as for example, the multiple neurofibroma (Hoekstra) and the retinal glioma. This, however, is probably exceptional. Certain "cancer families" are reported, in which the incidence through several generations is much above the average (Warthin). Certain statistics indicate that about 25 per cent. of patients with tumors, give a family history of tumors, but other figures are much lower, ranging from about 5 to 10 per cent. According to Bashford, cancer deaths occur in about 9 per cent. of males and 11 per cent. of females who live to thirty-five years or more, and this incidence would give a history of cancer in about one of every two families. If incidence be so high, it is impossible to say whether the occurrence of tumors in families is the result of heredity, or is due simply to the chance attacks within families due to the high general incidence rate. In the study of human disease, the difficulty of distinguishing dominant and recessive features and of determining hybrids is so great, that conclusions are often almost impossible. Statistics must therefore be clouded by a maze of factors, not the least of which is the uncertainty as to the cause and nature of tumor growth.

The study of animals is somewhat more productive of results, since pure breeds can readily be established. In mice bred by Murray from recent cancerous progenitors, the incidence of cancer was 18.2 per cent. as compared with 8.6 per cent. in others bred of more remote cancerous ancestry. Results about equally indicative of cancer heredity were obtained by Tyzzer. The number of animals in these two investigations is sufficiently small to interpose a considerable factor of error of random sampling. On the other hand, Maud Slye has made much more extensive observations, which include necropsies on over 40,000 mice with an incidence of over 5,000 non-experimental tumors. Ewing summarizes her results as follows:

"(1) The inheritance behavior of neoplasms is that of a Mendelian recessive. (2) Double cancerous parentage yields 100 per cent. tumor strains, except where some individuals die of infections before they reach the cancer age. (3) Single cancerous parentage yields heterozygotes (transmitting but not themselves developing cancer) in the first hybrid generation. These, whether inbred or hybridized with other heterozygotes, yield in the next hybrid generation non-cancerous, heterozygous and cancerous progeny, approximately in the proportion of 1 : 2 : 1. (4) The mating of a cancerous with a heterozygous individual gives approximately 50 per cent. cancerous and 50 per cent. heterozygous offspring. (5) Double non-cancerous parentage yields 100 per cent. non-cancerous strains. (6) The tendency to cancer, therefore, is inheritable, as no character except one which is hereditary can behave in this manner. This segregating out of a character is the test of heredity. (7) The tendency to tumors of specific organs and of specific types is also inheritable. For example, this stock has yielded strains of 100 per cent. lung

tumor, or 100 per cent. alveolar carcinoma of the mammary gland, or 50 per cent. liver adenoma, or 37 per cent. kidney tumor."

Wells in his admirable and extensive review of the subject emphasizes the fact that resistance to cancer is the dominant factor. This means that pure dominants and heterozygous hybrids should be resistant. Susceptibility is a non-survival factor and should therefore be a recessive. Resistance should be possessed by a large majority of the population and susceptibility by only a small minority. It seems likely that of those susceptible, not all necessarily develop tumors, even although they live to advanced years. The evidence available, supports the inference that the laws established by Slye are probably applicable to man, but the behavior of these laws in producing recessives and the fact that local influences, such as irritation, may be necessary as exciting causes, gives an encouraging aspect to the situation. Prophylaxis offers a promising field of endeavor.

SPECIAL TUMORS

CONNECTIVE TISSUE TUMORS

Introduction.—Many tumors placed in the group of connective tissue tumors are so classified for the sake of simplicity. The fibroma is the type tumor of this group but others diverge markedly from the type. Furthermore, these tumors are not all simple in structure, and combinations of tissue representing two or more types of tumors may appear. In this case combined names are employed such as fibromyoma, osteochondroma, etc., in each instance the major part of the tumor being represented by the second of the two names. Generally speaking, the group includes benign tumors, but in each instance where this is not strictly true the characters indicative of lack of benignancy will be noted.

Fibroma.—Tumors of this character are composed essentially of white, fibrous connective tissue and may originate in any situation where this type of tissue is found. They occur in the skin, subcutaneous tissue, fascias of various kinds including sheaths of muscle and nerve, periosteum, in the connective tissue of mucous membranes, and are observed also in solid organs such as the breast, kidney and ovary. The common tumor of the uterus is not as a rule a pure fibroma. Grossly, tumors vary considerably in size and may reach very large dimensions, may be single or multiple. In the smaller tumors measuring a few millimeters in diameter a capsule is often not found, but as the tumors increase in size they are as a rule very definitely encapsulated. The consistence is variable, but usually the tumor is very firm and is often spoken of as fibroma durum or hard fibroma. Some of the tumors are soft, particularly as the result of edema or degenerative change, and these are referred to as soft fibroma or fibroma molle. This distinction, however, has little practical value in determining the nature of the growth. The tumor cuts with considerable resistance, even when soft, and usually bulges above the cut surface of the surrounding tissue. Unless unusually well supplied with blood vessels the tumor both on the outer surface and on the cut section is pale. The bulging,

somewhat moist, pallid cut surface shows whorls of tissue giving the surface the appearance of "watered" silk. If a capsule be present the cut surface bulges beyond the capsule. Unusual vascularity, hemorrhage, degenerative and necrotic changes are likely to exhibit their characteristic alterations both upon the outer surface and upon the cut surface. The soft fibroma is likely to show a gelatinous cut surface. Microscopically, the characteristic cell is the connective tissue cell, which may appear either as a relatively young connective tissue cell or fibroblast, or the older type with longitudinally striated cytoplasm. The nucleus may be of oval or spindle form, and varies in chromatin density with the maturity of the cell. In any case, the section shows interlacing whorls of parallel cells and fibers which may be cut longitudinally, obliquely or transversely. Mitotic figures are extremely rare. Usually the tumor is very poorly vascularized and the larger vessels are carried in fibrous tissue septa which may divide the tumor into more or less definite lobules. The vessels are likely to follow finer division of the septa, which then appear in the form of a delicate reticulum, and ultimately communicate with very small vessels in the substance of the tumor. The finest vessels appear as vascular slits in the substance of the tumor but are by no means numerous. A few lymph spaces may be found and occasionally also nerve fibers, probably included as the tumor grows. Special stains show the fibroglia fibrils of Mallory. The cellular content of the tumor varies somewhat with its age. The younger tumors are rich in cells and show relatively little collagenous material, but as the tumor ages, the collagen increases in amount and the cells are relatively less numerous and usually compact. The capsule appears as strands of dense connective tissue, arranged circumferentially about the tumor and usually poor in nuclei. The surrounding tissue is likely to show some degree of compression.

Degenerative changes are not uncommon and the most frequent is hyaline transformation of the collagenous material. Mucoid degeneration may suggest an associated myxoma. Infiltration of small amounts of fat is sometimes observed. In the larger tumors necrosis is fairly frequent. Calcification is not rare. If the tumor be pedunculated, twisting of the pedicle may lead to passive hyperemia, hemorrhage and complete or partial necrosis. Surface tumors are subject to erosion and secondary infection.

Many of the tumors called xanthoma are really fibromata in which the cells are infiltrated with yellow lipid pigment, but in some instances the pigmented cells predominate and the condition is regarded as a xanthoblastoma (see Gauhl, Silberberg).

Fibroma may appear at any time of life but is more frequent in later middle life. The tumors arise insidiously and grow slowly. According to the usual criteria the fibroma is benign in character, but may produce serious disturbance of function owing to compression of, or traction upon, surrounding tissue. The sharp limitation of the tumor makes complete removal simple, but a few cases of incomplete removal have been followed by recurrence.

Combination of the fibroma with other types of tumor is common, such as the fibromyoma of the uterus and the fibro-adenoma of the breast. A fairly

common special variety of the fibroma is spoken of as cheloid or *keloid*. This is most common in the black race, and in the neighborhood of the face and hands where trauma may occur. The origin of the keloid is usually in scars. Grossly, it is a more or less nodular or lobulated mass, projected above the skin and showing the pale, glossy surface of a scar. Although movable, it is not encapsulated. Cross section shows a pale, glossy surface with very little suggestion of whorls. Microscopically, the mass is poor in cells and rich in collagen. Dense heavy bands of fibrils are separated by lines of more cellular material and the overlying skin shows the flat non-papillary appearance of cicatrization. Tendency to recurrence after removal is striking because of the disposition of this tumor to grow in scars, and removal necessarily leaves a scar



FIG. 146—Fibroma of muscle showing encapsulation and the "watered silk" appearance of the cut surface.

in its track. Small foci of lymphocytes are often seen in the keloid, suggesting that the lesion is inflammatory rather than neoplastic. Certain authorities look upon it as a hyperplastic scar, but it is tentatively regarded as tumor by most investigators.

Fibroma molluscum, von Recklinghausen's disease, or multiple neurofibromatosis is a condition in which multiple fibrous nodules in the subcutaneous tissue elevate the skin and often enlarge so as to project as pedunculated tumors. They may follow the course of cutaneous nerves, or be distributed asymmetrically over a large part of the body surface. They are sometimes painful or tender. In certain cases the overlying skin may be pigmented. The tumors vary in size from a diameter of a few millimeters to large masses several centimeters in diameter, and show no uniformity in the given case. Deep nerves and even visceral nerves may be affected. According to Verocay, Herxheimer and Roth all the supporting tissues of the nerve may take part

in the fibrous tissue multiplication, including peri- and endoneurium and the cells of the sheath of Schwann, one or other predominating in different specimens. In the case of cranial nerves, the meninges and even the glia may participate. Grossly, the tumors appear as somewhat soft fibromata. Microscopically, they are cellular with a variable amount of intercellular collagen, and are likely to show the inclusion of a few nerve fibers, but these do not multiply to form a part of the growing tumor. The tumor, therefore, should be called more properly perineural fibroma. As it increases in age the connective tissue may increase in amount and become hyalinized. *Plexiform neurofibroma* is more localized and affects more especially the head and neck. The tumors are likely to be large, of irregular, lobulated outline due to the plexiform arrangement of the connective tissue and the inclusion of more or less tortuous or coiled nerve trunks. Hereditary disposition is important in this disease. Various dysontogenetic manifestations may be associated in the cerebrospinal axis and other situations (see Winestine).

Nasal polyps occur most commonly in early life, as large, soft, pallid, gelatinous, pedunculated masses attached to the lateral walls of the nose near the openings of the accessory sinuses. Microscopically, they are covered by ciliated columnar epithelium and consist of edematous connective tissue, often infiltrated with lymphoid and endothelial cells and eosinophiles. The connective tissue cells are spindle form and stellate and are separated by edematous fluid. In sections the fluid is a granular, albuminous, acidophilic material in contrast to mucoid, which is basophilic. There is usually a history of chronic nasal catarrh or acute or chronic infection of the accessory sinuses, and it is probable that these growths are almost entirely inflammatory in character rather than true tumors. The mucous glands may become adenomatous in certain polyps or even adenocarcinomatous, and occasionally large cysts of epithelial mucus are encountered. Nevertheless, a true fibrous tumor of rare occurrence has been observed in the pharynx, called the juvenile nasopharyngeal fibroma. It is extremely firm and extends widely as it grows. It shows a considerable mixture of elastica with the fibrous tissue.

Chondroma.—The chondroma is made up either of hyaline or fibrocartilage. It is often difficult to differentiate it from ecchondrosis or hyperplasia of cartilage. Ecchondroses appear in connection with permanent cartilage, are multiple, of rather limited growth and reduplicate in their structure the cartilage from which they are derived. The chondroma, on the other hand, although it may appear as a multiple tumor, shows the departure from normal in structure and growth which is characteristic of tumors. Not infrequently the term enchondroma is used to distinguish the tumor from the simple hyperplasia. Kettle divides the chondromas into three classes: "(a) Those growing in relation to bones, especially the pelvis, the long bones and the bones of the fingers; (b) in situations where cartilage is normally present, such as the larynx; (c) in organs where cartilage is absent, chiefly the ovaries and testicles and salivary glands." The appearance of a chondroma may be preceded by local injury. In several instances a distinct hereditary disposition has been

noted. Grossly, the chondroma is a dense, solid tumor often lobulated and divided by connective tissue septa. It cuts with great resistance and shows a firm, pale, glossy cut surface in which lobulation is fairly distinct. Microscopically, the tumor shows irregularly disposed spherical or more rarely stellate cartilage cells, in lacunæ of varying size and arrangement. The cytoplasm occasionally shows vacuoles. In many tumors the areola about the cells is not clearly defined. The intercellular material may be the usual hyalin or a fibrillated fibrocartilaginous substance; occasionally elastic tissue is present. The vascular supply is carried in the connective tissue septa between the lobules. Various retrogressive changes may be present, but the most common is calcification. In fact, it is distinctly unusual to find a chondroma without some calcification present. Frequently the primary calcification is rapidly altered into true ossification, apparently under the influence of the capsular connective tissue which has the function of perichondrium. Mucoid degeneration is also common, but it is usually very difficult to decide whether it is a true degeneration or a mixture of chondroma and myxoma.

The chondroma may produce serious difficulties as the result of situation. For example, in the pelvic bones it may interfere with labor; in the larynx and trachea it may interfere with respiration. It may completely collapse a lung. The chondroma seems to have a greater disposition to recur after removal than the other tumors generally classified as benign. Situated in the ovaries, the testicle, and in the uterus and even in the breast, the chondroma is usually a part of a teratoma. The teratoma itself may be malignant, and metastases may show the development of chondroma. Careful analysis of cases, however, leads to the view that chondroma itself does not metastasize. Truly malignant forms of the chondroma occur as the chondrosarcoma.

Osteoma.—The osteoma is even more difficult than the chondroma to separate from hyperplasia and heteroplasia. Hyperplasia of bone occurs in connection with repeated traumatic insults, and more especially in connection with inflammation either of the periosteum or of the bone substance itself. In osteomyelitis, extensive and diffuse hyperplasia of the bone may occur. Similarly, inflammation of other structures, such as tendons, may lead to a deposit of bone in or along the tendon, as is well exemplified in rider's bone. Heteroplastic bone formation, as has been mentioned in the chapter on calcification, may appear in a wide variety of situations, usually, however, as a result of preceding chronic inflammation. In addition, a peculiar form of inflammation of the muscles called myositis ossificans shows true bone formation. The true osteoma must therefore arise in situations where it cannot be interpreted as of inflammatory origin. The pure osteoma is rare, but may occur in connection with either long bones, or flat bones such as those of the head. Deposits of bone in connection with inflammation are usually referred to as osteophytes. Exostoses are tumor-like projections from the surface of bones, whilst enostoses appear in the substance of the bone or project into the marrow cavity. Both these and the true osteomata may be made up of dense compact bone to form the eburnated variety, or of spongy bone to form the

spongy variety. Traumatic exostosis may occur at the site of fractures or in the margins of the alveolar processes following extraction of teeth.

Osteoma may appear as part of teratoma. Mixtures with other tumors of the connective tissue group, such as osteofibroma and osteochondroma, are more common than pure osteoma. Osteosarcoma occurs in several distinct varieties, to be discussed in the chapter on organs of locomotion.

Several tumor conditions may arise from the teeth and their anlage. The dentigerous cyst is usually of considerable size, made up in part of dentine and enamel and often contains more or less perfectly formed teeth. The odontoma is a tumor made up of masses of imperfectly formed teeth. The adamantinoma will be discussed with epithelial tumors.

Myxoma.—The true myxoma, a tumor of mucoid tissue such as that of the jelly of Wharton, is uncommon. It is derived from embryonal cells which have the capacity for forming connective tissue mucin. Epithelial tumors containing mucin are referred to as mucinous adenomata, mucinous carcinomata, etc. Connective tissue mucin, or mucoid, may appear in inflammatory tissue and in degenerations of fibroma, lipoma, chondroma, endothelioma and certain other tumors. Myxoma may constitute an important part of both teratoid and simple mixed tumors, and in fact is rarely found as an unmixed tumor. The commonest combination is with chondroma. True myxoma occurs in subcutaneous and subserous connective tissues, bones, along nerve trunks, in muscle, in the endocardium, and as a congenital tumor in or near the umbilicus. Grossly, the tumors are of variable size and may be pedunculated. They are usually lobulated, pallid, of soft elastic consistence and may be only partly encapsulated. They cut easily and from the soft, bulging, pale, gelatinous cut surface may be squeezed or scraped a tenacious, colorless mucus, soluble in dilute alkali and precipitated by weak acid solutions. Microscopically, the characteristic cells are spindle form and stellate, with long interlacing delicate cytoplasmic processes, separated by characteristic basophilic mucoid, either hyaline or granular. The proportion of cells and mucoid varies even in the same tumor. Blood vessels are contained in the septa between lobules and may be much dilated. Various retrogressive changes, especially hemorrhage, may occur. Mucoid may usually be differentiated from edema by ordinary stains but in case of doubt the mucicarmin or thionin stains may be employed. This is of importance in differentiating between an edematous fibroma and a true myxoma. The chemistry of mucoid has been discussed in the chapter on degenerations.

Lipoma.—The lipoma, a tumor composed of fat tissue, is of common occurrence. It is usually derived from preëxisting fat tissue, although certain instances occur in which it seems probable that connective tissue may undergo metaplasia to form fat. The most common situation is in the subcutaneous tissue, particularly of the neck and upper parts of the trunk. Nevertheless, such tumors may appear in synovial membranes, along nerve trunks, within the cranial cavity, in the kidneys and other viscera, including the heart. They are sometimes multiple and may even show symmetrical disposition in the

body. As a rule of moderate size, they may become extremely large and pedunculated. Excessive growth of fat around the kidneys may form very large perirenal lipoma, and sometimes the whole neck is involved from the face to the shoulders to produce the lipoma annulare colli. Grossly, the small lipomata may have only one lobule but as a rule, the tumor is a well defined multilobulated tumor, easily removed from the surrounding tissue but with only a thin fibrous capsule. It is soft, elastic in consistence and of the same color as normal fat, except in those instances where a rich admixture of cells of fibrous or other tissues tends to make the color lighter than that of normal fat. It cuts with ease and greases the knife, the cut surface being soft, bulging and greasy. Microscopically, the characteristic cell is the large signet ring cell of adult fat tissue.

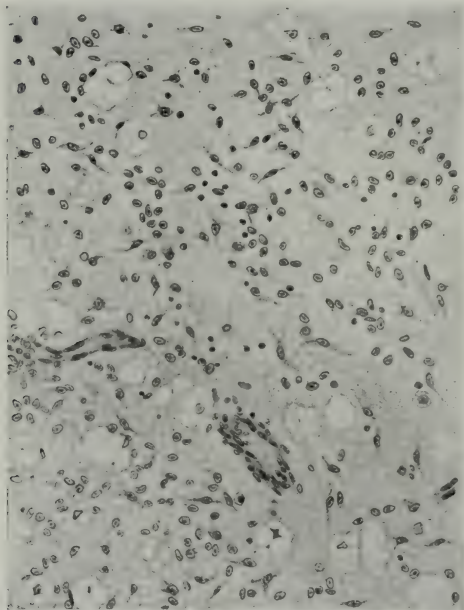


Fig. 147—Myxolipoma, showing granular mucoid between the cells.

Certain authorities maintain that the cells of lipoma are larger than those of normal fat tissue, but this is not supported in our experience. Sometimes, embryonal types of fat cells are observed, the cytoplasm studded with small vacuoles and with centrally placed round nucleus. Such cells are likely to be found in the margins of rapidly growing tumors. The septa dividing the tumor into lobules may be of fairly dense connective tissue and support the blood vessels of the tumor. Capillaries between the fat cells are not frequently observed; nevertheless, blood vessels may be fairly numerous and dilated. The same is true of lymphatic vessels. Mucoid degeneration, necrosis, and calcification may occur. In

retrogressing tumors, edema may appear, as is the case with fat atrophy in other situations.

The lipoma can usually be completely removed so as to prevent recurrence. Tendency to recurrence is especially notable in the retroperitoneal lipoma, even though the primary tumor shows no gross or microscopic evidence of malignancy. The damage done by a lipoma depends largely upon its location. Thus, pressure upon important organs as the brain by intracranial lipoma, pressure upon important tubes, such as the esophagus or intestinal canal, and pressure upon nerves may be of serious consequence. Lipoid degeneration and the deposition of the pigmented lipid of xanthoma may be observed.

The lipoma is not infrequently combined with fibroma to form a fibrolipoma. Other combinations may also appear. Lipoma may constitute a very large part of certain teratoid tumors such as those which occur in connection

with spina bifida. Lipoma may also be combined with sarcoma, more especially in retroperitoneal situations.

Chemically, the fat of the lipoma does not differ from normal fat in constitution or lipase content, but for some reason the fat is not utilized by the organism, and may even accumulate in increasing amounts in spite of progressive emaciation of the subject.

Angioma.—This is a tumor composed of either blood or lymphatic vessels, and is therefore designated as either hemangioma or lymphangioma. They are composed of the various cellular elements which normally appear in

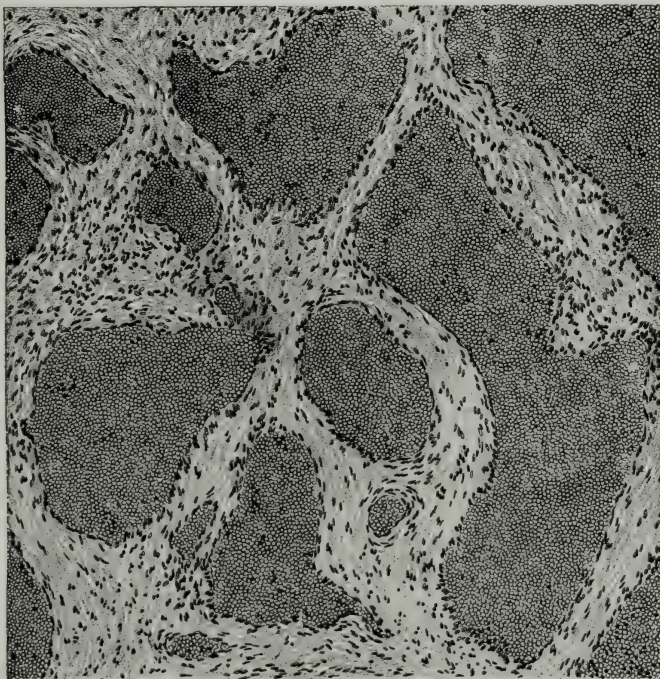


Fig. 148—Cavernous hemangioma of the orbit.

the vessel walls, thus forming tumors more organoid in type than those previously discussed.

Hemangioma.—Localized dilatations of large numbers of blood vessels may occur in connection with granulation tissue, or with varicosities due to stagnation of blood. Sometimes it is difficult to distinguish between these acquired dilatations and true hemangioma. As a rule, the hemangiomata are made up of vessels of capillary character but not necessarily of capillary size. Plexiform angioma, in which the dilated capillaries are elongated and plexiform, is likely to show venules and arterioles but the commoner tumors are more simple in structure. The hemangiomata are usually either of the simple variety, with vessels of small or moderate size, or the cavernous variety with large sinus-like vascular spaces. The simple hemangioma occurs as the birthmark on the skin, more particularly in the face (vascular nevus), but may affect

other situations including muscle, viscera and central nervous system. The "port wine" birthmark is said to contain venous blood and the "strawberry" mark arterial blood, but histologically the character is the same. These are to be regarded as simple congenital telangiectases, hamartomatous in type, but they may become blastomatous. They are composed of thin walled, blood containing vessels, of irregular size and shape, lined by endothelium and separated by a more or less cellular connective tissue. Although not encapsulated they are well defined. They occur in the corium immediately beneath the epiderm. If the intervacular tissue be richly cellular, the cells of endothelial type, the tumor is referred to as a hemangio-endothelioma.

The cavernous hemangioma occurs frequently in the liver but may be found in other situations. It is of congenital origin and is hamartomatous (see Moise), but rarely is said to become blastomatous. As usually seen, it appears immediately under the capsule of the liver as a small flat or slightly projecting mass, varying from the usual diameter of a few millimeters up to several centimeters. It is of deep red or purple color, soft, spongy and sharply defined although not always definitely encapsulated. The cut surface is spongy and retracts as the blood oozes out. Microscopically, it is made up of vascular sinuses of variable size and shape, with little fibrous connective tissue between. Fibrous septa may divide it into lobules. As with the simple angioma, this form may be combined with endothelial proliferation to form an angio-endothelioma.

As a rule, the hemangioma is of no importance except for its unsightliness upon the skin. Nevertheless, certain varieties may be serious. It may metastasize without striking alterations in its histology. In certain situations pressure may be serious; paralysis of the legs may be the result of an intraspinal hemangioma. One case has been observed in which an angioma of the liver attained enormous size, weighing with the small amount of remaining liver over sixteen kilograms. Hemorrhage from hemangioma of the renal pelvis has led to death.

Lymphangioma.—In principle the lymphangioma is like the hemangioma, save that it is composed of lymphatic vessels. The same difficulty arises as to differentiating telangiectases from true tumor growth. It may appear in the same situations as does the hemangioma. Three forms are described, the simple, cavernous, and cystic lymphangioma. The simple forms are likely to occur in the skin as colorless moles. The cavernous lymphangioma is best exemplified by a diffuse tumorous process in the tongue, macroglossia, and a similar condition in the lips, macrocheilia. The cystic form occurs in the neck as cystic hygroma, or hygroma colli cysticum. These masses are congenital and may interfere seriously with function. They are soft, spongy, pallid, and usually poorly defined. Differentiation from hemangioma is largely on the basis of the gross appearance, since the histological picture may be confused by operative hemorrhage in a lymphangioma or complete drainage of blood from the hemangioma. Congenital lymphangiomata may be observed in a variety of internal viscera.

Dilatation and elongation of lymph vessels in such conditions as elephantiasis, are due to obstruction of lymphatic drainage, and even though associated with progressive enlargement and progressive growth of connective tissue, the process is of inflammatory character.

Lymphangiomata may recur after incomplete excision, and rarely become malignant. The lymphangio-endothelioma probably originates as such, but may represent the malignant change of a lymphangioma. They may obstruct important tubes or may produce serious disturbance because of pressure.

Lymphoma.—The lymphoma is a tumor composed of lymphoid cells. Most tumors of the lymph nodes are either lymphosarcomata or are associated with blood diseases such as leucemia, and at times are difficult to distinguish from granulomata or chronic infection. Indeed a large proportion of the cases called simple lymphoma are probably of infectious origin. The simple lymphoma may appear in any of the subcutaneous chains or even in the deeper nodes, and has been observed in the parotid and other glands and in the viscera. It is slow in growth and after reaching a certain size may remain stationary for many years. Grossly, the tumor may be a single enlarged node, but usually is made up of several nodes more or less fused together. The tumors are firm and pale and when cut show a smooth, firm, gray surface with no degeneration or necrosis. Histologically, the architecture of the node is usually obliterated by a diffuse, poorly vascularized proliferation of small lymphocytes, without mitotic figures, but sometimes slightly invading the capsule. The chief danger is from compression of important viscera.

Chordoma.—This rare tumor arises from misplaced remnants of the notochord and is found in the skull near the base, in the region of the cervical vertebræ and near the coccyx. The tumors are usually of little significance but may produce serious symptoms. Grossly, they are soft tumors usually attached to the bone. Like the notochord, the tumors show large globular cells with vesicular cytoplasm, the so-called physaliphora cells, the intercellular substance being a homogeneous mass which takes the basic stain, probably because of content of mucoid. Careful gross and microscopic study is necessary for the diagnosis, since the myxochondroma and the mucinous carcinoma give somewhat similar microscopic appearances. Recurrence after operation is not uncommon (see Hirsch and Ingals, Lewis).

Myoma.—The myomata are tumors composed of muscle. They are of two sharply distinguishable types, the leiomyoma composed of smooth muscle, and the rhabdomyoma composed of striated muscle and muscle cells. They may be composed entirely of muscle or contain a considerable admixture of connective tissue.

Leiomyoma.—Tumors of this type may be found in any position where there is preëxisting smooth muscle, but are particularly frequent in the uterus. They also occur in the stomach, the intestinal tract, the skin, the bladder, in the prostate and not infrequently in the cortex of the kidney. Although sometimes single, they are usually multiple and vary in size from small tumors of a few millimeters in diameter to large tumors which in the uterus may attain

a weight of several kilograms. As a rule, however, the larger tumors are not pure leiomyomata, since a sufficient amount of connective tissue is included to justify the name of fibromyoma or myofibroma. The tumors are sharply defined and almost always encapsulated. They are more or less firm, depending in part upon the amount of connective tissue and in part upon the secondary degenerative changes. The color is likely to be somewhat darker than that of the surrounding muscle. They cut with considerable resistance and show a cut surface which exhibits the same "watered silk" markings, due to whorls of muscle tissue, as seen in the fibroma. The cut surface is softer than that in the fibroma, bulges, and is of the pale red color of muscle. The fibro-



Fig. 149—Multiple fibromyomata of the uterus. Note intramural tumor and submucous polypoid tumors. A cystic ovary is present.

myoma is often pearly gray in color. Microscopically, the essential cell is the smooth muscle cell, which, in the tumor, is likely to show a somewhat rounded instead of the normal sharp pointed end. The cytoplasm is acidophilic and not striated. The nuclei are elongated cylindrical rods, of the so-called sausage form, with rounded ends. Myoglia fibrils can be demonstrated in the cell cuticle by special methods. The cells are arranged in whorls and thus may appear in longitudinal, oblique, or transverse section, in all of which the acidophilic cytoplasm is striking. The character of the cells can usually be made out by ordinary staining methods, but in case of doubt the van Gieson or Mallory connective tissue stain may be employed. In the smaller, pure myomata there is practically no connective tissue between the cells, but as the tumors grow older, collagenous connective tissue fibrils, very poor in cells, can be demonstrated, and as age increases the amount of connective tissue may be

rich. Not infrequently, the connective tissue cells are the seat of edema. The tumors, as a rule, are poorly vascularized. Larger vessels are carried in the denser connective tissue septa. The blood vessels may, however, be fairly rich and the seat of some dilatation; as a consequence, hemorrhage into the tumor may result. The lymph vessels may also be the seat of extreme and extensive dilatation.

Degeneration of various kinds is common in the leiomyomata. Hyalin is frequent as are also fatty degeneration and hydropic infiltration. Calcification, necrosis and inflammation are also observed. Cyst formation may follow necrosis or hemorrhage.

The combination of leiomyoma and fibroma is very common, particularly as the fibromyomata of the uterus. These tumors are soft in the early stages but may become very dense from the amount of connective tissue present. Histologically, connective tissue may be in fairly dense bands throughout the tumor or, as is more commonly the case, closely intermingled with the muscle cells. There also occurs, more particularly in the uterus, a combination of myoma with adenoma, the so-called adenomyoma. This tumor is likely to appear in the posterior wall of the uterus and is not characteristic grossly. Microscopically, glands similar to those of the endometrium are found, intermingled with the muscle tissue and cells, which resemble those of the tunica propria of the endometrium. Sometimes, the tumors are richly provided with lymphatic vessels which may multiply and dilate to form the lymphangiomoma. The same is true of blood vessels which help to form the hemangiomoma. Malignant change is uncommon.

Rhabdomyoma.—These tumors may originate in preëxisting striated muscle, when they are called homologous, or may be observed in situations where there is no striated muscle, when they are called heterologous. Although the tumor is a rare tumor under any circumstances, the homologous rhabdomyoma has been reported more often in the heart than in other situations. The cases reported as occurring in skeletal striated muscles are in many instances of doubtful nature. In the heart, the association with other congenital disturbances such as diffuse sclerosis of the cerebral cortex, as well as a study of the tumor itself, make it probable that it is due to congenital misplacement of embryonic striated muscle. The homologous tumor rarely attains any considerable size but may be 2 or 3 cm. in diameter. It is relatively soft, of spongy consistence and paler than the surrounding muscle. It is usually well defined but not definitely encapsulated. Microscopically, it is made up of muscle fibers and muscle cells. Fibers are likely to be of narrow type as seen in embryonic striated muscle and in the transmission bundles of the heart. The transverse striations are often not very clearly defined and are usually fairly well separated from one another. The nuclei are centrally placed in the fiber. Longitudinal striations may or may not be clearly defined. The muscle cells are usually large spherical cells, with large vesicular nucleus and a clearly defined large nucleolus. The cytoplasm is likely to be edematous and, in many instances, muscle rods resembling the transverse striations of the fibers are

observed within it. The interstitial tissue is made up of adult connective tissue, or of richly cellular embryonic type of connective tissue. Vascularization is irregular. The muscle usually exhibits little in the nature of a true sarcolemma. Glycogen has been demonstrated in one case, thus indicating the embryonic character of the muscle. Sometimes the fibers may be seen to branch. Mitotic figures are observed in some cases. This type of tumor is essentially benign (see Wolbach, Kawamura).

Heterologous rhabdomyomata may be observed in a variety of situations where muscle does not normally occur, and are usually a part of a teratoma, although in some instances the other elements of teratoma may not be appar-

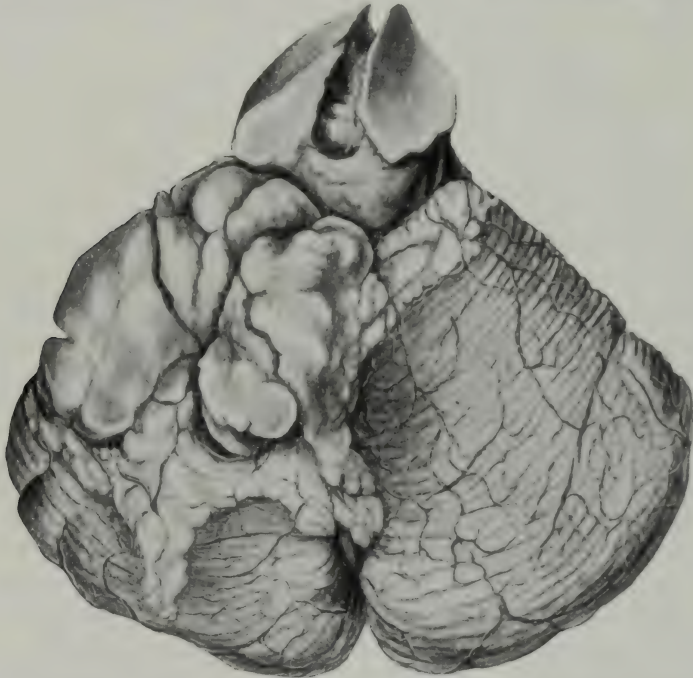


FIG. 150—Large glioma of the cerebellum, invading right lobe and to a lesser extent middle and left lobes.

ent. Such tumors are seen in kidneys, in the testes and other parts of the genito-urinary tract, in the esophagus, in the parotid glands and other situations. The diagnosis is microscopic and depends upon finding striated muscle as observed in the homologous rhabdomyoma. Metastasis from the teratoma may occur, and in the secondary nodules the same type of muscle cells and fibers are found, although sometimes the striation disappears and the muscle resembles very closely ordinary smooth muscle. A teratoid tumor of this sort is occasionally observed in the vagina of children or the cervix uteri of older women, and is referred to as the sarcoma botryoides of Pfannenstiel.

Tumors of Nerve Tissues.—Tumors of nerve tissues, when regarded in the embryological sense, should be classified as epithelial, since the nervous system is derived from ectoderm. The cells of the tumors, however, show differentiation in varying degrees and therefore are morphologically unlike epithelium.

Few of these tumors show any tendency to metastasis, but many of them are invasive, and by virtue of their situation may produce serious symptoms. It is therefore difficult to regard them as strictly benign, but they usually lack the characters necessary for grouping them as malignant.

Glioma. (Neuroglioma).—The glioma is composed of neuroglia cells and fibers. It occurs most commonly in the brain, but is also seen in the spinal cord and occasionally in the roots of the cranial nerves. Neuroglia is also found in teratoid tumors. Focalized gliosis, or hyperplasia of neuroglia, is not uncommon and may be confused with glioma. The glioma is usually a solitary tumor varying in size from one to several centimeters in diameter, but may grow so as to occupy the space of a cerebral hemisphere. Although probably due to some embryonal disturbance of development, a history of trauma in nearly 10 per cent. of the cases suggests that injury may play a part; the hypothesis of traumatic origin cannot be regarded as proven. It is usually situated in the interior of the brain but may project into the ventricles or upon the outer surface. It is poorly defined and grows by replacing brain tissue; its size may increase intracranial pressure. It is likely to be softer than the brain substance. Its color may be the same as the surrounding substance, but brain markings are obliterated. It is sometimes very pale or, if richly vascularized, is pink or streaked and dotted with red. Hemorrhage is common, as is also necrosis. Cyst formation as the result of hemorrhage or necrosis is frequent, and may also be due to the production of spaces lined by ependyma-like cells. Microscopically, as pointed out by Bailey and Cushing, the glioma may be composed of a wide variety of cells, and there have been described twelve types of glioma. The cell type may represent any of the cells which occur in the differentiation of the primary neuro-epithelium to the more mature forms of astrocytes, pineal, choroidal and ependymal cells. Thus, the size and character of the tumor cells vary, and some tumors may contain many glia fibrils and others few or none. In a general way, the prognosis is better in those tumors where the cells are more highly differentiated. Further details of cell type are given in the chapter on nervous system. A scattering amount of connective tissue may be present, derived from blood vessels. The blood vessels are of variable size and occasionally angiomatous. Frequently perivascular spaces are found, and sometimes dense masses of glia fibrils surround the vessels. Owing to the lack of encapsulation and to destructive and invasive growth, operation is often followed by recurrence.

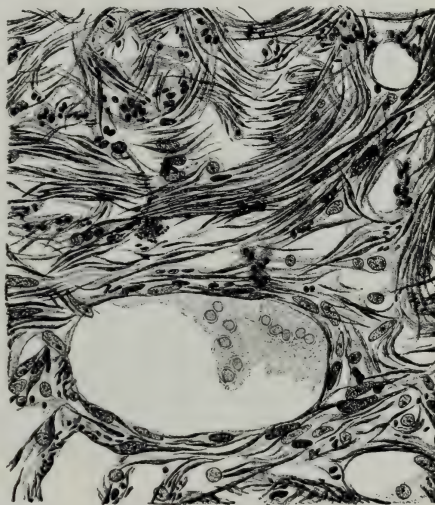


FIG. 151—Fibrillar glioma stained by phosphotungstic acid hematoxylin to show fibrils. Astrocytes are obscured by the large number of fibrils.

Occasionally, true malignancy is indicated by the occurrence of metastases. The microscopic appearance is not materially altered, and it seems preferable to refer to these as metastasizing or malignant glioma rather than gliosarcoma.

The neuro-epithelioma is a glioma of cellular type, which histologically shows few if any glia fibrils, and an arrangement of cells to form rosettes. The rosette may or may not have a central lumen into which minute rods may project, the primitive rods and cones. From the central portions cuboidal cells radiate to fuse with the surrounding cell mass. This is the usual glioma of the retina, but a similar tumor may be encountered anywhere in the central nervous system. Heredity appears to be important in connection with this tumor. Not uncommonly both eyes are affected.

Neuroma.—Tumors of nerve tissues are uncommon. Arising from the central nervous system, peripheral nerves and sympathetic system, they may be found in practically any part of the body. They are usually a mixture of nerve cells and nerve fibers. The cellular tumors may be made up in large

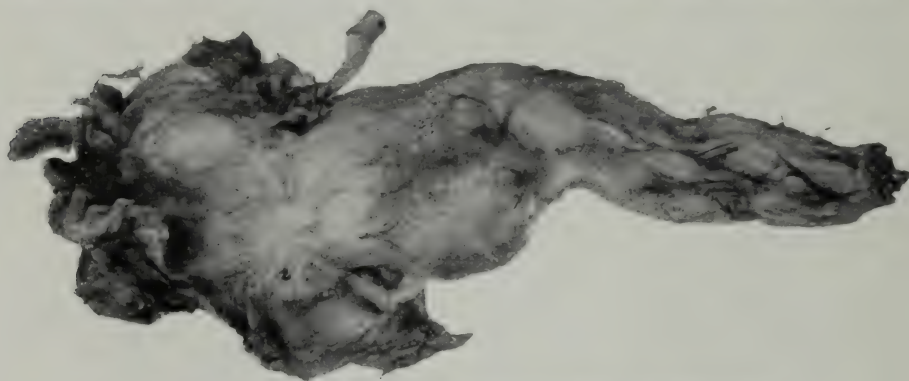


Fig. 152—Neuroma of the sciatic nerve. Army Med. Mus. 18090.

part, or almost entirely, of cells in any stage of development from those resembling the primary neuro-ectodermal cells to those of adult type. The cellular tumors are given various names indicating their nature, thus leaving the term neuroma to cover those tumors composed largely of nerve fibers. The most primitive tumor is the neuroblastoma. A group of tumors has been reported, arising principally in the sympathetic system, under the names neuroblastoma and neurocytoma, because the fibrils were not stainable by the usual method for neuroglia. Bailey and Cushing, on the basis of newer methods have found that these are, in numerous instances, the type of glioma to which they give the name medulloblastoma. Nevertheless, rare cases are found in which the tumor is made up principally of unipolar neuroblasts. Various degrees of differentiation may be found between the true neuroblastoma and the ganglioneuroma, which is made up largely of ganglion cells, sometimes multinucleated, and nerve fibers, usually non-medullated. The paraganglioma is characterized by the presence of cells of the paraganglionic chromaffin system. This tumor is not pure and occurs in the adrenal, retroperitoneal ganglia and in the carotid gland. Of these tumors the neuroblastoma is the

one most likely to be malignant, and the mixture of neuroblastomatous elements with the other tumors may determine malignancy. The mature ganglioneuroma is usually benign.

The neuroma is composed principally of fibers, but examination of the whole tumor should demonstrate cells. In the discussion of regeneration of nerves, it was pointed out that a group of investigators consider it probable that nerve fibers may form independently of nerve cells, probably from cells of the sheath of Schwann, but it seems more likely that nerve fibers are only formed by parent nerve cells. If the former view be correct, it would be possible to have tumors composed entirely of fibers, as is maintained by Froboese; if, as seems more likely, the latter view be correct, nerve cells should be demonstrable. Technical difficulties may make it impossible to decide the question as regards all neuromata, but with ordinary examination, such tumors often fail to show nerve cells in a given section. The neuromata may be made up of medullated or non-medullated nerves, and are called accordingly myelinic or amyelinic. The former occur in the course of peripheral nerves and the latter involve the sympathetic system. They are essentially benign tumors save for their situation, which may lead to pressure symptoms or interruption of impulses. The Weigert myelin stain can be used for the myelinic variety, but the diagnosis of the amyelinic fibers is usually by exclusion of other possibilities, since often these fibers do not take the stains for axis-cylinders. It seems probable that such tumors are really a part of ganglioneuromata and that complete examination will disclose ganglion cells. In all instances they should be differentiated from the neurofibroma discussed under the heading of fibroma.

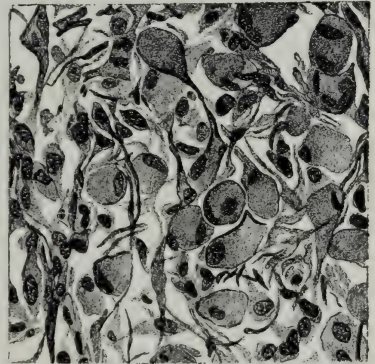


Fig. 153—Small section of a ganglioneuroma, showing a cellular portion of the tumor.

In amputation stumps a tumor-like growth of nerves may be found, called amputation neuroma or false neuroma. This growth represents an elongation of the nerve fibers due to excessive regeneration, the new fibers interlacing and coiling to form a painful mass. Obviously this is not a true tumor.

Endothelioma.—The endothelioma is a tumor composed of endothelium. The employment of the term endothelium in this connection includes the endothelium of blood vessels, lymphatic vessels and various serous cavities. The classification which we employ is not embryological, but is based upon resemblance between the cells comprising the tumors and the tissue cells of the adult. Therefore, the discussion as to whether the lining of the serous cavities is mesothelium or endothelium need not be considered. Accepting this assumption, there is still a great difference of opinion as to whether the endotheliomata constitute a large group of tumors or a relatively small group. At one time there seemed little doubt that numerous tumors might properly be classified as endotheliomata, but later studies have identified several of these

as of other origin, so that the group is growing smaller. The morphology of the endothelial cell as it appears in tumors is not characteristic, and on the one hand may resemble fibrous connective tissue cells and on the other hand epithelium. It is, therefore, necessary to trace the development of individual tumors or groups of tumors so as to know exactly where they should be placed. Even with this information at hand, it is often difficult in a given slide to determine whether the observer is dealing with endothelium or with some other type of cell. Endotheliomata have been described in the pleura and peritoneum, the lymph nodes, bones, ovaries, uterus, stomach and in certain other situations. The nature of these tumors, that is, as to whether they are benign or malignant, varies considerably in the individual case. Not infrequently the tumors, although not encapsulated, show no great invasive capacity and do not metastasize. On the other hand, certain instances are reported in which

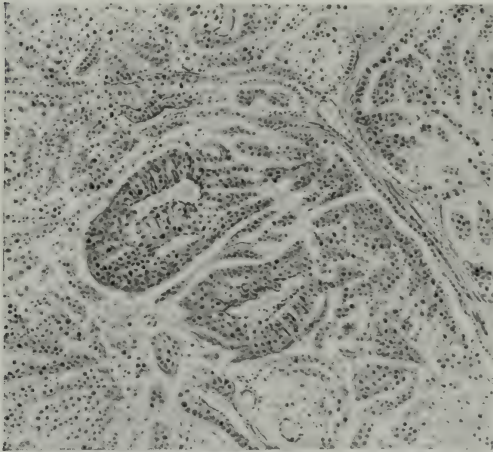


Fig. 154—A peritoneal endothelioma, showing trabeculae, sheets of cells and vascularization.

metastasis appeared in the neighborhood of the original tumor. The endotheliomata are fairly dense, solid tumors, not well defined, but in the serous cavities may project as nodular or papillary growths. They cut with considerable resistance and show a pale, firm cut surface. Derived from lymphatic or from blood vascular endothelium there may be, in some of the tumors, a considerable proliferation of blood vessels even to a point where angiomatous character is very apparent, thus giving rise to the terms lymphangio-endothelioma and hemangio-endothelioma.

Necrosis is not likely to be severe except in the larger tumors of the serous cavities. Microscopically, the characteristic cell resembles the endothelial cell. It is large, generally spherical, with a faintly acidophilic cytoplasm. The nucleus is centrally disposed, vesicular and may show a nucleolus. Mitotic figures are not unusual. The cells are usually spread in rather dense sheets, with little tendency to isolation of individual cells. The connective tissue supporting framework may be so arranged as to divide the tumor into lobules, and proper staining will usually show a certain amount of stroma between the cells. The cells may be arranged in whorls either independently or around blood or lymphatic vessels. Sometimes the surrounding tissue shows only pressure, and sometimes distinct invasion may appear. The cells of the tumor may be flattened, especially in the cell whorls, so that in cross section they appear to be of spindle form.

The dural endothelioma has long been referred to as a type of this tumor, but the studies of Mallory and of Cushing make it clear that such tumors

originate in the cells of the arachnoid. Mallory suggests the term arachnoid fibromatosis and Cushing the term meningioma. This is based on a comprehensive study of the embryology of the dura and arachnoid, in which it has been shown that the Pacchionian bodies originate from arachnoid, penetrate the dura, and may give rise to tumors in which collagenous material and fibroglia, as well as elastica are clearly demonstrated by special methods. From this same type of tumor originates the psammoma, the difference being that in the latter, whorls of cells show central laminated calcification, but this does not alter the fundamental character of the tumor.

The studies of Robertson indicate that most, if not all, the so-called endo-

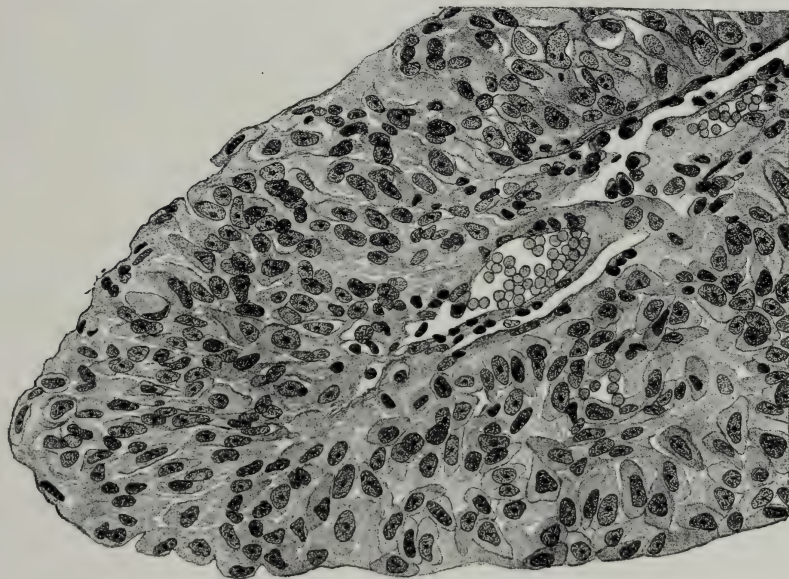


Fig. 155—A detail of the tumor shown in fig. 154, to show cell characters of the sheets of cells.

theliomata of the pleura are extensions from, or metastases of, primary cancer elsewhere.

A rare endothelial tumor is the *perithelioma*. It cannot be said definitely whether this tumor originates in the perithelial endothelium or in the lymph vascular or blood vascular endothelium. The tumor is composed essentially of blood vessels, around which are thick sheaths of cells morphologically endothelial in character.

The *cylindroma* is composed of cells of endothelial or epithelial character, which in various places in the tumor are arranged to form cylindrical or globular spaces occupied by acidophilic hyaline material. This may represent a secreted material or hyalinized necrotic cells. Sometimes the material is mucinous. This type of tumor often occurs as a part of the common mixed tumor of the parotid. In this situation the nature of the cells is in great doubt, some believing them to be epithelial, others endothelial, and still others maintaining that the tumor originates in misplaced cells of the blastomere,

which, as the tumor grows, differentiate to form the round cells as well as the cartilage and mucoid cells commonly found in these tumors.

The *cholesteatoma*, an unusual tumor of the cerebral meninges and spina cord, is sometimes regarded as endothelial, but as pointed out in the chapter on diseases of the nervous system is really epithelial.

MALIGNANT CONNECTIVE TISSUE TUMORS

Introduction and Classification.—The malignant connective tissue tumors are called sarcomata. These tumors comprise two groups, those in which the cells are immature and without important differentiation, and those in which differentiation although incomplete is sufficient to produce a similarity to adult tissues such as fibrous connective tissue, muscle, cartilage, bone, etc. There is unanimity of opinion in calling the first group sarcoma, but opinion is divided in reference to the second group. The latter are often so much like the fibroma, myoma, chondroma, osteoma, etc., and the history so often indicates that malignancy is superimposed on a preëxisting benign tumor, that certain authorities would employ the term sarcomatous fibroma, sarcomatous chondroma, etc. Nevertheless, the majority prefer not to complicate a terminology already established, and in view of the uncertainty of transformation, discussed earlier, it is more desirable to name these more mature forms fibrosarcoma, osteosarcoma, myosarcoma, etc.

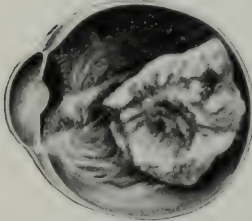


Fig. 156—Sarcoma of the eye (not a melanoma) showing fleshy character and several hemorrhages.

The undifferentiated forms include principally the round cell sarcoma and the spindle cell sarcoma. Round cell sarcomata include small round cell and large round cell varieties, although the occurrence of the latter form is now in some doubt. The spindle cell tumors include the small spindle cell and the large spindle cell sarcomata, but a more or less intermediate form occurs called the oatcell sarcoma. There is in addition a third form called the giant cell sarcoma, characterized by the appearance of multinucleated large cells, but the main mass of this tumor is made up either of round cells or spindle cells; the tumor is a subvariety of either of the simpler forms. The melanotic or black sarcoma is one composed of connective tissue cells of either round or spindle form, which have sufficiently differentiated to form pigment, such as that found in the choroid coat of the eye. We prefer to treat of this as one of the undifferentiated forms, since the differentiation is functional rather than morphological.

The sarcomata of both general groups exhibit, in varying degrees, all the features of malignancy, namely, invasive and destructive growth, metastasis (characteristically but not exclusively by way of the blood stream), cachexia, and recurrence after removal. The more immature forms, except in the case of the giant cell sarcoma, are generally more highly malignant than the differentiated forms, although many of the latter may also be distinctly malignant.

Although the sarcomata occur in early life more frequently than do malig-

nant epithelial tumors, they are essentially tumors of late middle and advanced life. Frequently there is a history of a slowly growing tumor, whose growth abruptly becomes rapid, but many of them grow rapidly from the time they are first noticed.

Gross Morbid Anatomy.—As the name indicates, the sarcoma is a fleshy tumor. It is usually bulky, but may be small. It is more or less adherent to surrounding structures, and the overlying skin or other part, shows distended vessels. There is usually capsule formation, as a rule incomplete. The immature forms are of soft consistence, pink in color, poorly defined, partly encapsulated, and show distended superficial blood vessels. They cut with about the resistance of living muscle, and show a bulging, soft, somewhat friable, bleeding, pallid, pink or red cut surface, in which small and large blood vessels can be seen; necrosis and hemorrhage are commonly present. The more highly differentiated forms vary from the consistence of fibroma to that of bone, are less well vascularized and usually less subject to secondary degenerative changes. Reactive inflammation of the surrounding parts is mild subacute or chronic.

Microscopical Appearance.—

There are certain features of fundamental importance which will be elaborated in the discussion of individual sarcomata. The features common to these tumors are certain characters of cells, stroma and vascularization. The

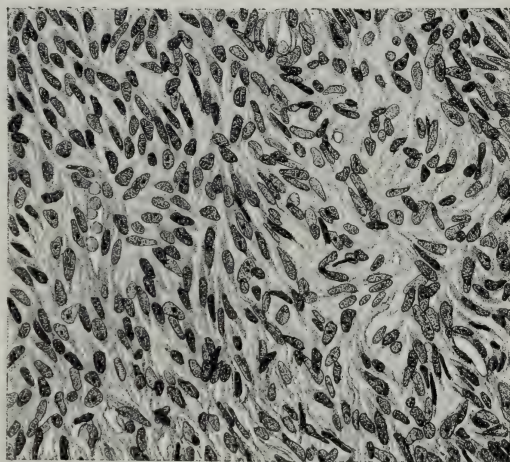


Fig. 157—Spindle cell sarcoma showing cell type.

tumor cells are immature and as such are likely to be only slightly acidophilic or even basophilic. Cell outline may be obscure and the tumor sometimes appears to be made up of masses of syncytial character. The nuclei are large and vesicular. Mitotic figures both typical and atypical, bipolar or multipolar, as well as amitotic division, are common in freshly fixed material. Multinucleated cells are often seen. The supporting framework is supplied in part by the host, but inasmuch as the tumor cells are of connective tissue type they furnish the greater part of the fibrils. The term stroma usually refers to that part of the connective tissue support furnished by the tumor cells. The stroma may occur as dense bands which ramify through the tumor or even divide it into alveoli, or as fine reticular fibrillæ between the tumor cells. The presence and character of the stroma were formerly thought to be of importance in differentiation of cancer from sarcoma, and in identifying different types of sarcoma, but this view no longer holds, since fine stroma may be demonstrated by special methods in many types of malignant and non-malignant growth. The blood vessels are derived ultimately from the

host, which certainly provides all the more important vessels. From the smaller branches, new capillaries grow by the same process of endothelial multiplication as occurs in granulation tissue. As tumor growth progresses, the capillary endothelium may be much attenuated. In the latter case, vascular slits are found in the tumor with only an occasional endothelial cell between blood and the tumor cells. In the spindle cell tumors the cells are often arranged at an angle to the vascular slit, parallel rows of cells and nuclei in the form of a wide palisade ranging from the vessel as though they had been "combed." The more gross indications of invasiveness are seen in sections which include the surrounding tissue.

Retrogressive Changes.—In spite of the rich vascularization of most of the immature tumors, necrosis is common. It is usually in small areas, although the greater mass of the tumor may be involved. Consistent with the vascularization, hemorrhage is frequent. Other retrogressive changes are seen in the more mature forms, such as hyaline and mucoid degeneration in the fibrosarcoma. Owing to the rapid growth of sarcomata, the surrounding tissues may be more or less devitalized, thus removing local resistance to growth; erosion on skin surfaces and into body tubes is common, resulting in infection and inflammation of the tumor, with further necrosis, sloughing and even gangrene.

Histogenesis and Etiology.—Although malignant tumors as a class grow principally by centrifugal growth, many of the sarcomata show both centrifugal and centripetal growth; in other words, all the cells appear to be active in enlarging the tumor. Sometimes the reactive inflammation in the surrounding tissues appears to show a transition between normal surrounding connective tissue and sarcomatous cells, as though the host were helping to enlarge the tumor. It is generally believed that such transformation of cells does not occur, and that the tumor grows entirely by multiplication of its own cells. Injuries of various kinds may precede the manifestations of sarcoma, as blows on a bone preceding bone sarcoma, or chronic inflammation leading to cutaneous sarcoma. The importance of the injury is not so well established in reference to sarcoma as carcinoma. Experimentally, Murray has found a sarcoma in the site of repeated tar injections. Bullock and Curtis produced sarcoma of the liver of rats by introduction of the larva of *tenia crassicolis*, and evidence is further accumulating that chronic irritation may lead to sarcoma. The Rous chicken sarcoma is transmissible by filtrates of the tumor, but only if the soil be prepared by the use of kaolin, thus indicating that some minor injury of the field is important. Sarcoma sometimes develops in the base of the tuberculous skin ulcers (lupus), and it appears that tuberculous lymphadenitis may become sarcomatous. Congenital sarcomata are almost certainly due to embryonal cell isolations, misplacements or faults of development, and it is possible that these phenomena play a part in adult sarcomata. These suggestions are all hypothetical and subject to much further investigation.

Spindle Cell Sarcoma.—The spindle cell sarcomata are commonly found in the bone, periosteum, subcutaneous connective tissue and in the fascias,

muscle and tendon sheaths. More rarely they are observed in the uterus, ovaries, breast, testis, thyroid and other situations in the body. This tumor typifies the fleshy character of sarcomata. There are, however, various gradations between the spindle cell sarcoma and the fibrosarcoma so that on the one hand, very firm tumors may be encountered and on the other soft tumors, with intermediate grades between. Microscopically, the cells may be large, small or intermediate and unusually there is found the oatcell sarcoma with a short broad spindle form. Extremes are easily recognized, but intermediate types of cells are divided according to personal preference of the observer. The differentiation into large and small spindle cell sarcoma is of little practical value. Nevertheless, it is stated that the tumors arising from fibrous connective tissue are likely to show small cells, while those originating from periosteum and smooth muscle are more likely to show large forms. The cells are of elongated spindle form, rich in cytoplasm, arranged closely together with a small amount of collagen between. The nuclei are large, vesicular and of long ellipsoid form. The cells are arranged in bundles of various size which ramify irregularly through the tumor, sometimes giving rise to a whorled appearance of the cut surface, and in the microscopic section showing cells cut in various planes. If this fact be not borne in mind, the tumor may appear to be made up of both round cells and spindle cells. Vascularization is usually rich and typical "combing" of cells is very common. Large spindle



Fig. 158—Spindle cell sarcoma showing type of vascularization, "combing" of cells and mitotic figures.

shape multinucleated giant cells are often observed in the large spindle cell sarcoma, but are not so frequent in the small cell variety. A fine stroma may be provided by the spindle cells but is never very rich. Occasionally, however, masses of dense connective tissue fibrils may divide the tumor into more or less distinct nodules. In epithelial organs, it is very difficult to state whether the spindle form cells are of connective tissue origin or are epithelial in character, and the diagnosis of sarcoma in certain situations is often open to considerable doubt. The difficulty of distinguishing histologically between granulation tissue and sarcoma has led to mistakes in diagnosis, but the intimately intermingled inflammatory changes in the former usually indicate its nature.

Small Round Cell Sarcoma.—This type of tumor is unusual but appears occasionally in the connective tissue of muscles, fascias and in certain other situations. This tumor represents the most complete anaplasia of all the

sarcomata and correspondingly is the most malignant. It grows rapidly and metastasizes widely and rapidly. Critical examination makes it appear that many tumors reported as being of this sort are really small spindle cell forms, and that others are lymphosarcomata. What we believe to be differential features between this tumor and the lymphosarcoma will be described subsequently. The glioma shows similar cells but special staining demonstrates the neuroglia. The cells are small round cells quite uniform in size, with a small amount of cytoplasm and relatively large, moderately vesicular nuclei. Although well vascularized, secondary changes, particularly necrosis, are likely to be extensive, and hemorrhage is a frequent complication. A fine

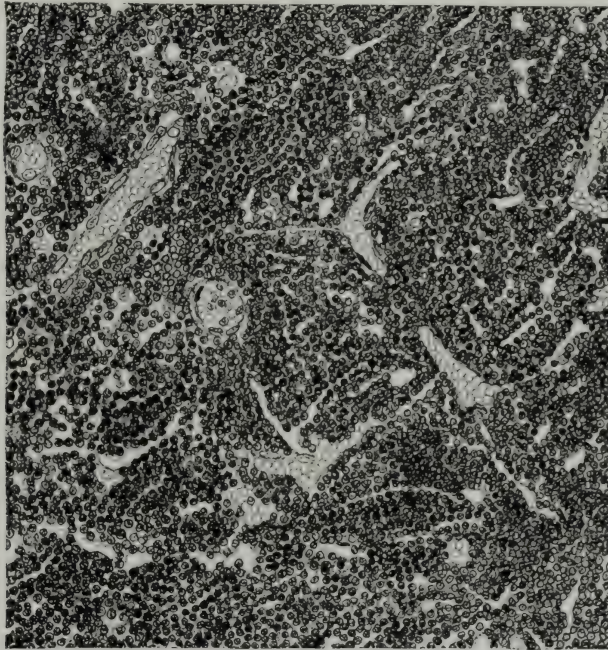


Fig. 159—Small round cell sarcoma.

reticulum may be demonstrated between the cells but is usually very scanty. Not infrequently, however, the tumors may be alveolated by the growth of fairly dense connective tissue septa.

Large Round Cell Sarcoma.—This tumor also occurs in connection with fascias, particularly of muscle, and appears sometimes in the viscera. Although highly malignant, it is not so markedly so as the small round cell sarcoma. It is much more likely to be an alveolated tumor. The cells are large, with somewhat richer cytoplasm than in the small cell tumor, nuclei are correspondingly larger and more vesicular. The cells tend to be arranged as discrete polyhedral, cells with extremely scanty stroma. Formerly, this tumor was supposed to be common in the testicle, but investigation has shown that the testicular tumor in practically all instances is derived from primary testicular

epithelium and is not a sarcoma. The large round cell tumors of the thyroid are probably also entirely epithelial in character.

Giant Cell Sarcoma.—There is no tumor made up entirely of giant cells, although several varieties of sarcoma may show a considerable number of giant cells. By common usage the term is now applied to tumors, most commonly of bone, in which giant cell formation is very prominent. There are three important forms of this type of tumor, the giant cell epulis of the jaw, the giant cell sarcoma of the ends of long bones and of spongy bones, and a tumor of periosteum which shows a large number of giant cells. The giant cell epulis appears as a rule in the alveolar processes of the jaw, usually after extraction of teeth. It is a slowly growing tumor which in the majority of cases is small, but it may attain considerable size. It is of almost bony hardness

and as a rule can be removed completely. The firm, pale, fairly well defined tumor cuts with much resistance, and shows a pale, poorly vascularized but rarely necrotic, cut surface. Microscopically it is made up of masses of small spindle cells intermingled with a very large number of giant cells. These giant cells are large and contain a dozen or more nuclei scattered irregularly in the middle of the cell. The blood vessels are usually in the form of small vascular spaces which sometimes show the typical sarcomatous arrangement of spindle cells around the vessel. A histologically similar, but grossly different tumor is the giant

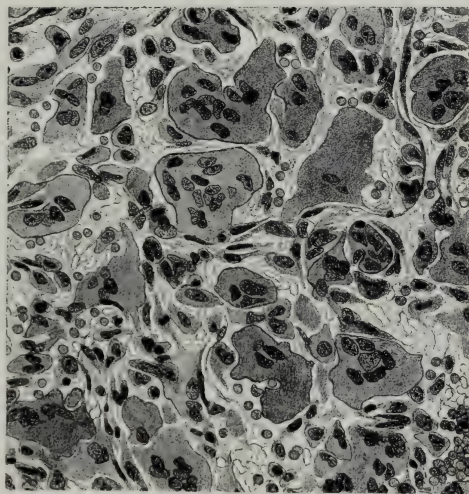


Fig. 160—Giant cell sarcoma, showing the types of giant cells.

cell sarcoma of the ends of the long bones and of spongy bones. This tumor frequently has a history of preceding injury. It grows with moderate rapidity, invades bone and occasionally may pass through the bone into the soft parts. It is somewhat more invasive in character than is the giant cell epulis of the jaw. Grossly, it usually presents a soft, jelly-like, red mass, and hemorrhage into this soft mass is often present. Capsule formation is entirely absent. The mass is friable, cuts easily and shows a soft bulging cut surface. Microscopically, it is a fairly well vascularized tumor composed as a rule of spindle cells, intermingled with which is a large number of multinucleated giant cells similar to those seen in the epulis. Although these two tumors are usually called sarcoma they lack many of the features of malignancy. The epulis rarely invades deeply and is usually removable completely, although in some instances local recurrences appear. The tumor of the long bones and spongy bones can be removed by local treatment such as thorough curetting of the bone, and although recurrence may be observed a second or third

operation is usually successful. The name benign giant cell tumor is preferable to sarcoma. The epulis does not show metastasis and Ewing states that he has never seen metastasis from the giant cell sarcoma of the bones. Nevertheless, metastasis has been reported. Mallory maintains that the giant cells in these tumors are foreign body giant cells of endothelial origin, although in the ordinary section foreign body inclusions are rarely encountered. These cells show no fibers or fibrils and on this basis are different from the essential cells of the tumor. Mitotic figures are rare in both these tumors. The periosteal giant cell sarcoma is essentially a spindle cell sarcoma which grows rapidly, invades the soft parts, and is likely to show metastasis. The giant cells of this type of tumor differ from those in the preceding form in that they resemble more closely the spindle cells of the tumors. Multiple mitotic figures are commonly observed in these cells and the cells produce fibers and fibrils. They are fundamentally and essentially like the cells of the tumor and are of tumor origin.

Melanotic Sarcoma. Melanoma.—The melanoma is only provisionally



Fig. 161—Melanosarcoma of the scalp.

included among the sarcomata because the exact nature of the cells concerned is unknown. The tumors are composed of cells which produce a pigment classified among the melanins. The tumors usually arise in preëxisting masses of pigment-bearing cells, more particularly the pigmented moles or nevi of the skin, the choroid coat of the eye, the pia arachnoid and the rectum or anus. There is considerable difference of opinion as to the nature of the cells in moles, some maintaining that they are endothelial, others that they are epithelial and others that they represent original mesoblastic chromatophores. The pigmented mole of the skin is a flat or slightly elevated, sometimes papillary, well circumscribed, pale yellow to dark brown area, appearing as a birthmark or as a later development. Histologically, it is made up of rounded cells with oval or round vesicular nuclei and a moderately rich cytoplasm from which a few collagen fibers may extend, the whole forming cord-like or large, generally spherical masses in the corium. The cytoplasm contains fine dark brown granules, which do not give the iron reaction. Varying numbers of the cells show no pigment. This is to be regarded as a hamartoma rather than a true

tumor. These moles usually remain quiescent throughout life, but as the result of trauma, irritation, or independently, may become invasive and metastasize widely. The metastases may appear in any part of the body and usually suggest the picture of a disseminated sarcomatosis. The individual metastases may or may not be pigmented. Histologically, they contain little or no stroma, are fairly well vascularized, show very thin walled vascular slits among the closely apposed tumor cells. The cells are usually large, round, with moderate amount of cytoplasm and relatively large oval or round vesicular nuclei. Sometimes mitotic figures are frequent. It will readily be understood that the classification of the malignant tumor depends upon knowledge of the nature of the cells in the mole. The mole has no exact counterpart in normal histology of adult tissues. Conclusive proof that the cells are either endothelial or epithelial is lacking, and it seems wise to regard them as remaining elements or direct descendants of the mesoblastic chromatophores. This assumption offers reasonable ground for classifying the tumor as sarcoma. It is invasive and metastasizes both by lymphatics and by the blood stream. Kreibich, however, describes a case in which the tumor seems to have originated in the pigmented cells of the epiderm.

A most important tumor of this group is that arising in the choroid coat of the eye. This is usually a spindle cell tumor, but may be made up of round cells. If excised early, recurrence may be avoided, but metastasis may begin before definite clinical signs appear. The organ most commonly affected by metastases is the liver, which may be enormously enlarged by the metastatic tumors; numerous other parts of the body may also be the seat of metastases. Histologically, the spindle cell melanomata resemble closely the spindle cell sarcoma save that pigmentation is present. Large parts of a given metastasis or entire nodules may be free from pigment, but as a rule, they are so deeply pigmented as to be black in the gross specimen.

Melanomata are also said to take origin in the rectum and in the adrenal. In the latter situation, it is possible that a pigment producing ferment is elaborated, as has been indicated in the chapter on pigmentations. It is likely that the rectal tumors really arise in the skin of the anus. In the

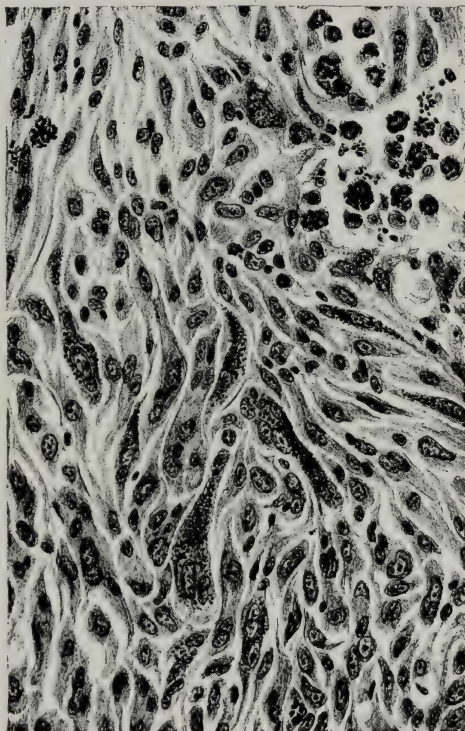


FIG. 162—Melanotic spindle cell sarcoma of liver. Pigment appears in fine granules in tumor cells and in coarser granules in phagocytic endothelial cells.

same chapter, the common occurrence of melanuria in cases of melanosarcoma has been discussed, a condition in which some precursor of melanin is excreted in pale urine, the urine subsequently becoming dark brown or black by the addition of oxidizing agents or upon standing in the air, due to the formation of melanin. An admirable discussion of the entire subject of melanoma, including derivation of cells, modes of origin, clinical and pathological features, is given by Dawson.

Fibrosarcoma.—In clinical and pathological features, this type of tumor stands midway between the fibroma and the spindle cell sarcoma. It is invasive but grows comparatively slowly; although circumscribed, a capsule is poorly developed or absent. Histologically, it differs from the spindle cell sarcoma in a distinctly richer content of collagen fibers, either diffusely scattered or arranged in bands. The cells are more condensed but larger than those of the fibroma; multinucleated cells are occasionally present. Mitotic figures are not common. "Combing" of cells about thin walled vascular slits can usually be made out. Metastasis may occur late in the course of the tumor but is not likely to be widespread. The diagnosis of malignancy is often difficult in those tumors which approach more closely to the fibroma.

Chondrosarcoma.—Grossly, this tumor resembles closely the chondroma, but may show more distinct invasiveness. Microscopically, it differs from the spindle cell sarcoma in that the matrix is hyaline cartilage. It differs from the chondroma in its richer cellular content, many of the cells being of spindle form and arranged in sarcomatous fashion. Briefly, it may be regarded as a more or less intimate mixture of the two types of tumor. Forms are met in which the tumor appears as a chondroma with only a few areas resembling sarcoma; on the other hand, the tumor may be essentially a spindle cell sarcoma with few and irregularly interspersed areas of cartilage.

Osteosarcoma.—Malignant tumors containing bone usually arise from bones, particularly the femur and tibia, but may appear in soft parts. These bone tumors arise from endosteum or bone substance rather than from periosteum, although bony sarcomata may arise from periosteum. Osteosarcoma is more common than osteoma. Irregular masses of true bone or an osteoid tissue, a bone-like mass poor in lime salts, characterize the tumor. Like the chondrosarcoma the amount of bone formed is inconstant. The cellular parts are like spindle cell sarcoma, but round cell tumors may be encountered. The more nearly the tumor approaches the osteoma, that is the more bony, the less likelihood of metastasis; the converse is true of the more richly sarcomatous tumors.

More common than the preceding two forms is a combination of both to form the osteochondrosarcoma, and this is not uncommonly accompanied by myxoid tissue to form the myxo-osteochondrosarcoma. In these instances care must be taken to exclude mixed or teratoid tumors. In any given instance the metastases may be like the original tumor, or show a single element as osteoma, chondroma, or sarcoma. This matter is more fully discussed in the chapter on organs of locomotion.

Myxosarcoma.—This malignant form of the myxoma is found in the same situations as the myxoma, namely subcutaneous and subserous connective tissues, intermuscular septæ, nerves, bones (marrow) and meninges. A congenital form with admixture of lipoma, fibroma and spindle cell sarcoma occurs. The undifferentiated sarcomata often show mucoid degeneration, which forms confusing pictures. The myxosarcoma is highly invasive and metastasizes widely. The histological picture is that of a highly cellular myxoma, well vascularized and with irregular sized large spindle cells, characteristic perivascular arrangement and numerous mitotic figures. Much more

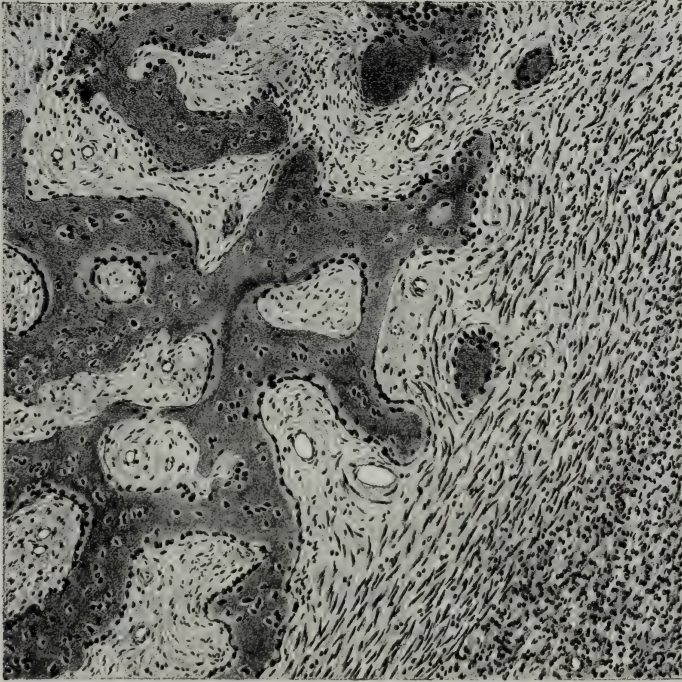


Fig. 163—Low power drawing of an osteosarcoma.

common are the forms in which chondromatous or chondro-osteomatous elements are also present.

Liposarcoma.—Rarely, lipoma may apparently metastasize without histological changes indicative of malignancy. The unmixed liposarcoma is rare, and usually appears to be a transformation of a preëxisting lipoma. With gross invasion and dissemination, the histological picture shows embryonic types of fat cells with multiple small fat globules and centrally disposed nuclei. Many of the cells show marked anaplasia to the undifferentiated spindle cells of a sarcoma. More common is the mixed retroperitoneal sarcoma which may be very largely made up of liposarcoma with variable degrees of anaplasia, and often combined with malignant chondroma, myxoma, etc.

Angiosarcoma.—This term is usually applied to a sarcoma provided with numerous, wide, vascular spaces. The angioma is, however, more an embryonal

fault of development than a true blastomatous tumor. Malignant changes rarely occur, but when they do are often accompanied by no important change in the histology. Malignant forms, probably originating as such, are seen in the form of angio-endotheliomata, the endothelium originating in perivascular spaces, and not in the endothelium, of the vessels concerned. Vascular sarcomas are likely to show necrosis of cells remote from the vessels, leaving a sheath of cells around the vessels; these are often incorrectly called perithelial angiosarcomata, but are simple vascular sarcomata with secondary necrosis. The use of the term angiosarcoma has little justification on morphological or genetic grounds, as the tumors to which it is applied are either sarcomata with secondary necrosis, or endotheliomata of particular form.

Myosarcoma.—Myomata of the uterus and of the intestine may occur as malignant tumors. It is believed by many that these represent malignant change of preëxisting benign myomata, but Ewing is inclined to regard them as primarily malignant. The term is practically limited to tumors of smooth muscle, since the rhabdomyoma is only malignant when occurring as a part of mixed congenital sarcomata. The leiomyoma may metastasize with little histological evidence of malignancy and the secondary nodules appear morphologically benign. The most characteristic are tumors in which the cells are of irregular shape and size, with large or hyperchromatic and often multiple nuclei, apparently muscle cells because of the rod-like or sausage shaped nuclei and non-fibrillated cytoplasm. These are usually richly vascularized, often with large cavernous vascular spaces and typical “combing” of cells from the vessels. Grossly, they are soft red tumors, necrotic, hemorrhagic, clearly invasive and often showing metastasis.

Malignant Tumors of the Hematopoietic System.—These include the lymphosarcoma, the chloroma and various forms of the myeloma, which will be taken up in connection with special diseases of the hematopoietic system.

The malignant possibilities of the glioma and the neuroma have been considered in the discussion of those forms.

EPITHELIAL TUMORS

Introduction.—Epithelium in its growth derives support from connective tissue, and nutrition from blood vessels. Tumors composed of epithelium must also have supporting tissue and vascular supply, and as the epithelial proliferation progresses the connective tissue and blood vessels must grow accordingly. If support and nutrition are not sufficient, degenerations or necrosis occur. Epithelium may derive nutrition as it penetrates lymphatic and tissue spaces, but extensive tumor growth cannot occur in this way. As surface epithelium proliferates beyond the area of surface to be covered, it becomes folded above the surface and, as it grows, connective tissue support and vascular supply are provided. In this fashion a papillary tumor arises. Growing from duct and gland surfaces it may become infolded into the tissues to produce gland-like spaces, which also must have support and nutrition. Thus, the adenoma is formed. Solid growth in the form of masses or bundles of cells occurs prin-

cipally in the malignant epithelial tumors, but this also cannot progress independently of support and nutrition. The epithelial tumors then are really combinations of epithelium, connective tissue and blood vessels. They are sometimes called fibro-epithelial, but such a term is supererogatory since from all points of view the epithelium is the essential tumor element.

The identification of epithelium in tumors is not without certain difficulties, particularly if it be conceded that such cells may assume a spindle form. Certain features, when present, are of importance, such as the presence of intercellular bridges, keratinization, intracellular mucin, intracellular hyalin, and the absence of fine stroma between the individual cells.

Secondary changes are not uncommon, such as fatty and other forms of degeneration. In the rapidly growing tumors, more particularly those which are malignant, necrosis is common and widespread due to the failure of the blood supply to keep pace with the epithelium and perhaps to other factors. Infection and inflammation occur, since many of the tumors, such as the papillomata, are superficial and others may erode upon surfaces.

There is often much difficulty in distinguishing between blastomatous growth of epithelium and hyperplasias. The latter occur as the result of inflammation and may produce papillary outgrowths resembling true papillomata. In the margins of ulcers of the skin, of the intestinal canal, etc., the epithelium may undergo hyperplasia and infiltrate a short distance into deeper tissues. This may go on to actual cancer formation, but the exact stage of transition is impossible to define with exactness, and confusion is easily possible. Inflammation of glands may produce microscopic pictures closely resembling certain forms of adenoma.

Because of the limited number of types, epithelial tumors can be discussed in smaller space than connective tissue tumors. This is no indication of relative importance or incidence, for epithelial tumors are extremely common and of the utmost importance.

BENIGN EPITHELIAL TUMORS

Papilloma.—This type of tumor grows characteristically from surface epithelium, but may also originate in epithelium lining glandular ducts and acini; papillomata may even appear upon serous surfaces and are then covered with endothelium. The core or papillæ of supporting connective tissue may be large or small, broad and flat or long and narrow, non-branching, simply branching or branching to form multiple divisions. This connective tissue is continuous with that of the region from which the papilloma arises, and may be either moderately or richly vascularized. The base may be co-extensive with the tumor or the latter may represent a polypoid mass attached by a single, more or less narrow, peduncle. The “hard” papilloma is covered with stratified squamous; the “soft” papilloma is covered with either transitional epithelium, simple or stratified columnar epithelium. These old terms, hard and soft, are being displaced by more exact terminology such as squamous epithelial papilloma, columnar epithelial papilloma, etc. The color and con-

sistency of the tumor depend upon the thickness and density of the covering epithelium and the vascularization of the papillæ, as well as incidental secondary changes.

Microscopically, the papillary arrangement is usually clearly indicated, but since the section is but one plane of a branching mass extending in two



FIG. 164—Large papilloma of the anus.

planes, or three diameters, various papillæ may be cut obliquely or transversely so as to show isolated islands of connective tissue surrounded by epithelium. Stratified squamous epithelium may show various degrees of keratinization up to marked hyperkeratosis in which thick, horny masses of keratinized cells project from the apices of the papillæ. In the interstices of the tumor a concentrically laminated mass of keratinized cells may form the so-called epithelial "pearls." The intermediate cells may show the inclusion of hyaline globules, the so-called Russell fuchsin bodies. Cell bridges may be

much more prominent than in normal epithelium. Mitotic figures may be found in strictly benign tumors; any supposition that their axes are differently placed than in malignant papillomata is not sufficiently well founded to be of diagnostic import. The simple or stratified columnar epithelial papillomata may show ciliated cells, goblet mucinous cells or various types of cellular degenerations. Desquamation seems more frequent in these than in squamous papillomata. Mitotic figures may also appear in this form of papilloma.

The squamous or transitional papillomata appear on skin surface, mouth, pharynx, larynx, esophagus, vagina and neighboring parts of cervix uteri, urinary bladder, renal pelvis. The cylindrical cell papillomata may be found in the nose, stomach, intestinal canal, gall bladder, uterus and Fallopian tubes. Metaplasia may determine the appearance of squamous papillomata in places normally covered with columnar epithelium. The superficial position and projection of papillomata subject them to trauma; injury and infection are common and may predispose to malignant change.

Malignant transformation of a papilloma is usually indicated by infiltrative growth of the epithelium about the base. The papilloma of ovarian cystoma is infiltrative early in its course, breaks through the

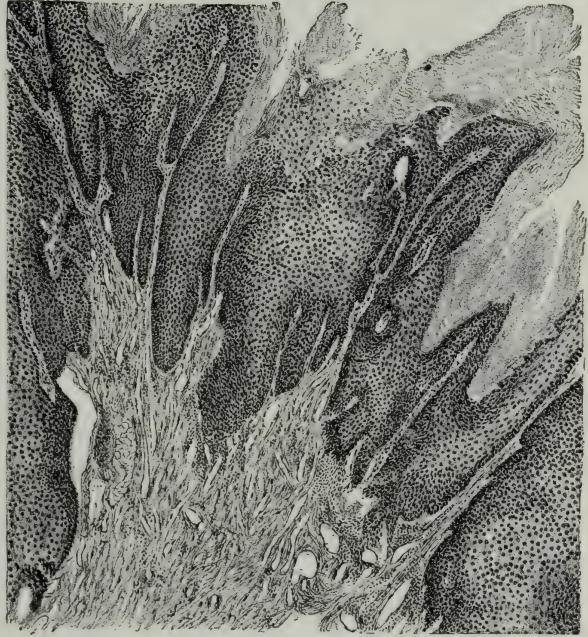


FIG. 165—Low power drawing of a squamous papilloma, showing fine connective tissue villi covered by stratified squamous epithelium with superficial hyperkeratosis.

ovary and extends widely over the surface of the peritoneum. This may show no clear evidence histologically of malignancy, but usually there is found definite invasive proliferation of epithelium. The papilloma of the urinary bladder may recur repeatedly after excision and yet show no histologic evidence of malignancy. On the other hand, the growth may be so wild and invasive that a diagnosis of papillary carcinoma may be made without hesitation. The production of papillary growths in cysts and glandular spaces will be referred to in discussing adenoma.

Irritative and inflammatory hyperplasias may closely resemble papilloma, and in the individual instances may be quite indistinguishable from true tumors. Thus, in the neighborhood of chronic catarrhal inflammations and around ulcers, papillary outgrowths may be observed. The nasal polyp may be papillary and is probably of inflammatory origin. The common wart of the

skin is morphologically a papilloma but can be transmitted by a filtrate, as shown by Wile; it is thus either of infectious or chemical origin. The acuminate condyloma or venereal wart, occurs on the external genitalia as a papillary growth of epithelium due to irritation such as that of gonorrhea. Molluscum contagiosum may produce pedunculated tumor-like masses, undoubtedly of infectious origin, with curious, large, vesicular epithelial cells containing the so-called molluscum bodies made up of a mucoid or keratoid material. Cutaneous horns and other types of hyperkeratosis are not likely

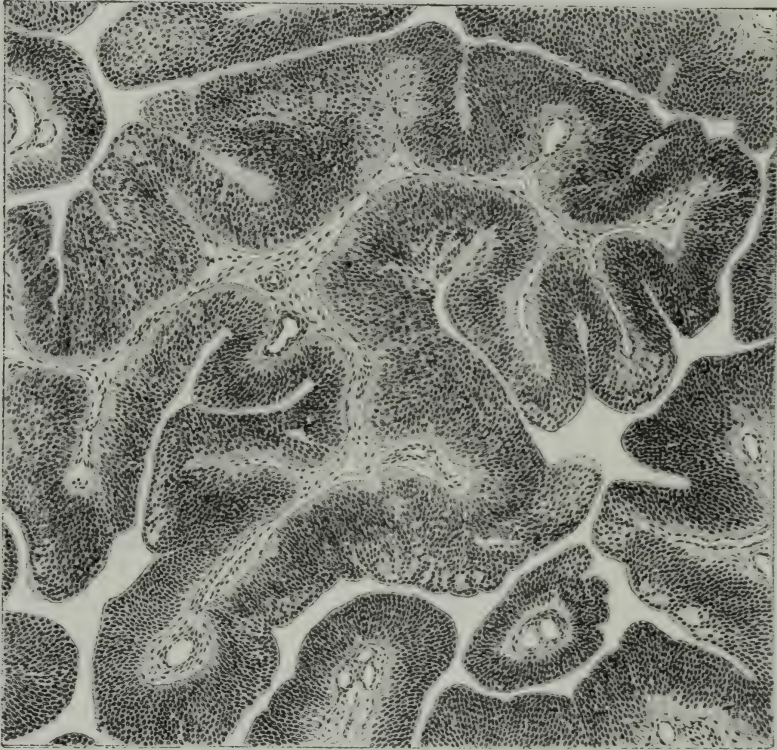


FIG. 166—Papilloma of the urinary bladder—transitional epithelium.

to be confused with true papillomata. Irritants may produce papilloma as is the case with papilloma of the bladder in aniline workers, which is not only of much scientific interest but also is of importance in industrial medicine.

Adenoma.—The adenoma is a tumor which in its growth reduplicates glandular tubules or acini or both. As with epithelial growth elsewhere, there must necessarily be a certain amount of connective tissue supporting framework provided. This sometimes is differentiated to form a tunica propria and practically always shows the formation of a basement membrane. Adenomata are practically always derived from tissues in which there is preëxisting glandular substance, although certain forms appear which are undoubtedly due to embryonal displacement or faults in development. Probably the commonest

situations are in the prostate, the thyroid gland, and the female breast. They are not uncommon in the skin where they arise from sweat glands or oil glands, in the kidney, the prostate, the adrenals, the pancreas, intestines and uterus. In certain situations it appears that inflammation may play an important part in the development of true tumorous adenomata, and it is well known that gland-like proliferation may occur in connection with inflammation of glandular tissues and organs. Thus, adenomatous proliferation in the breasts is not uncommon in chronic inflammation, and most of the cases of adenoma of the liver show an associated and perhaps causative chronic inflammatory process,

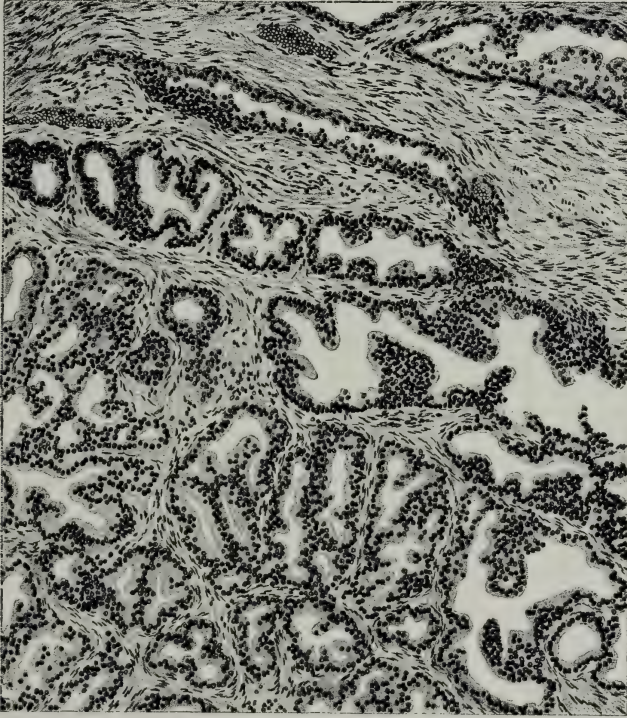


FIG. 167—Adenoma of the prostate, showing papillary infolding of lining epithelium.

cirrhosis of the liver. Grossly, the adenoma may be intraglandular or polypoid in form. The intraglandular forms appear as rounded nodules which may be more or less lobulated; they are practically always circumscribed and usually encapsulated. The polypoid forms may be flat or elevated, round or lobulated, and attached either by a broad base or a small peduncle. The consistence depends upon the amount of admixture of connective tissue but as a rule these tumors are fairly firm. They cut with moderate resistance and the cut surface may be simply a dull, flat, slightly bulging cut surface, sometimes with gray stroma and yellowish-white nests of acini, or if the acini are sufficiently large, is spongy. Microscopically, the tumor may be a solid adenoma, a tubular adenoma, in which the acini are of tubular form, or an alveolar

adenoma in which well developed acini appear. The solid forms in which there are cell masses with only slight differentiation into acini, are more likely to be seen in connection with adenoma of the liver, the adrenal, sebaceous glands and sometimes the thyroid gland. The acini of the adenoma usually lack uniformity in size, and are frequently more irregular in outline than are normal acini. The identification of the basement membrane is often of considerable aid in distinguishing between truly benign and malignant forms of adenomatous tumors. The connective tissue is usually moderate in amount and does not show any characters that would distinguish it as blastomatous. It may be richly or only moderately vascularized. In the breast, however, it is likely to be rich in amount, and the usual adenoma of the gland is so rich in fibrous tissue that the term fibro-adenoma or even adenofibroma is justified. The

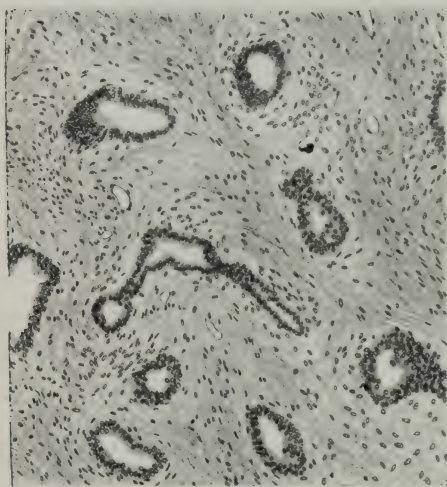


FIG. 168—Fibro-adenoma of the breast.

lining cells of the spaces may be low or high, cuboidal or columnar, and usually are in a single layer but may show a certain amount of multiplicity and stratification. Certain authorities maintain that the presence of multiple layers of epithelium in the acini indicates a disposition to malignant change, but according to Kettle and numerous others, this view is not justified. Nevertheless, it seems reasonable to suppose that when the epithelium grows in multiple layers, is thrown up into folds, or constitutes solid masses within the acinar space, epithelial growth must be regarded as going on more actively than in other simpler forms of this tumor. When it can be

demonstrated that the basement membrane is broken through by the epithelial growth, so that the latter spreads out into the surrounding tissue in the form of cords or solid masses, malignant change has begun. Such malignancy may, of course, be entirely local and removal of the adenoma be followed by no recurrence. The differentiation of this type of adenomatous cell is indicated both pathologically and functionally, because in adenoma of the liver bile may be formed, in adenoma of the thyroid colloid is commonly formed, and in adenoma of the gut and other mucous membranes mucin is formed. The production of secretory products by the cells of the adenoma may dilate the acinar spaces so as to form cysts, and the adenoma then becomes a cystadenoma.

The cystadenoma, then, is an adenoma in which the accumulation of fluid in the spaces has led to cystic dilatation. The cystadenoma may be either a true tumor or may be the result of tumor-like fault in embryonal development, as manifested in the congenital cystadenoma of the kidney and similar proc-

esses in the liver and in certain other situations. Cystadenoma may occur in any situation in which adenoma occurs, but among the most common is the cystadenoma of the ovary. Here two important types are found, namely, the pseudomucinous glandular cystadenoma and the papillary serous cystadenoma. In the former, cystic spaces several millimeters in diameter form a tumor of the ovary, reaching several centimeters or more in diameter. The content of the cyst is a gelatinous material referred to as pseudomucin. This takes the acid stain and only grossly resembles mucin. Histologically, there is a delicate, poorly developed, supporting framework, with the large glandular

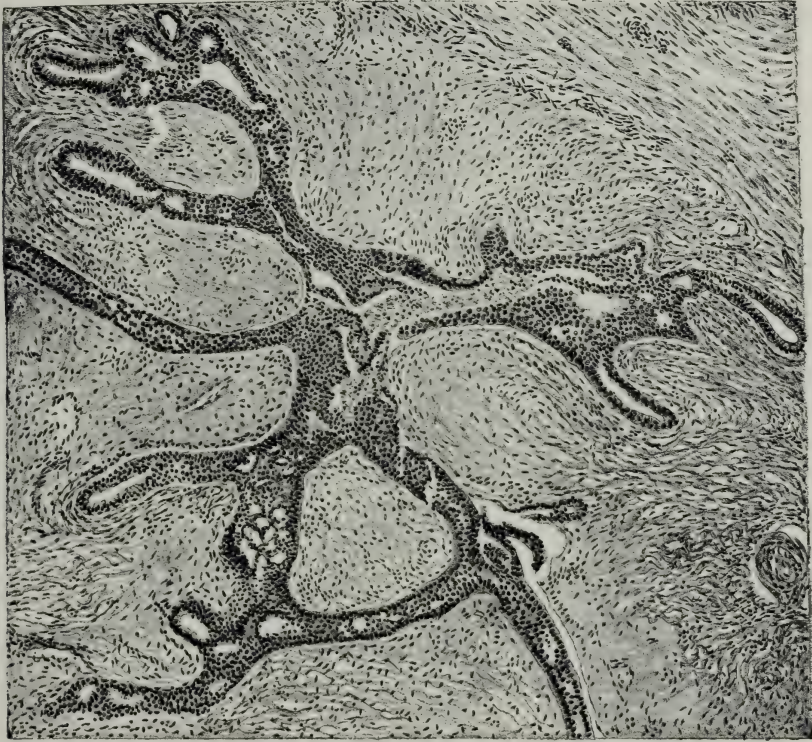


FIG. 169—Intracanalicular fibro-adenoma of the breast. The bulbous connective tissue papillæ distort the outline of the large acinus.

spaces surrounded by more or less flattened, low, cuboidal or almost squamous epithelium. The papillary cystadenoma shows the formation of papillæ extending out from the lining of the cystic spaces. These papillæ branch in an intricate fashion so that they very largely fill up the cyst space. The content of these cysts other than the papillæ is usually a thin serous fluid.

Papilla formation in various types of adenoma is fairly common. This may be exhibited in the form of dense, flat papillæ as seen in the intracanalicular fibro-adenoma of the breast, where the large, dense papillary masses of connective tissue fill up the entire lumen, leaving simply narrow strips of double layers of epithelium from apposed sides of the acini. The papilliferous cystadenoma of the ovary is one of the best examples of very intricate branching

of papillæ within an adenomatous growth. In this case, it is accompanied by cyst formation. Many adenomata show papillæ without true cyst formation. In this case, it appears that the epithelium lining the acini grows to such an extent that it can no longer lie flat along the outer circumference of the acinus. It then folds inward to produce papillary ingrowth into the acinar spaces. Only where the papilla formation is marked, is it customary to add the name papilliferous to indicate a growth of papillæ.

MALIGNANT EPITHELIAL TUMORS

Introduction.—The malignant epithelial tumors are the carcinomata or cancers. They may originate from stratified squamous epithelium to produce



FIG. 170—Fungating carcinoma of the cecum.

the epidermoid cancers, or from cylindrical epithelium to produce the adenocarcinoma or in undifferentiated form the carcinoma simplex. Whereas the benign epithelial tumors show more or less coördinate growth of epithelium and connective tissue, in the malignant forms the epithelium usually outstrips the connective tissue growth; these tumors are essentially epithelial as represented by multiplication, invasion, and metastasis of epithelial cells. The amount of associated connective tissue growth determines the consistency; hard cancers are called scirrhus cancers and the adjective may be used as a noun by changing the spelling to scirrhus; soft cancers are referred to as medullary; intermediate forms are not qualified by special terms. Scirrhus and medullary are used especially to indicate gross characters, but are also associated with well defined histological characters. Cancers are invasive

and poorly defined. From the point of view of invasion and metastasis the epidermoid cancers are not so highly malignant as the cylindrical cell cancers. The rôle of inflammation and irritation in the development of tumors has been discussed, but nowhere is it so well illustrated as in the growth of cancer. Ulcers of the skin, such as chronic leg ulcers, cutaneous ulcers in wearers of the Kangri basket, ulcers of tongue or lip due to irritation of teeth or smoking, etc., are likely to be complicated by the development of epidermoid cancers. Chronic gastric and intestinal ulcers may be the basis for cylindrical cell cancers. The experimental sudan-oil, tar and spiroptera cancers have already



FIG. 171—Multiple metastatic nodules of a gut carcinoma in the lymphatics of the mesentery.

been discussed. The situation, time of occurrence and history of human cancer stresses the importance of avoiding chronic irritation.

Cancer is a disease of advanced life, occurring particularly between forty and sixty years of age; this does not exclude the possibility of occurrence in later or earlier life. Indeed cancer of the new born has been reported, but care should be taken in these instances to exclude mixed tumors. According to Borst, cancer occurs in females more often than males in the proportion of six to four, owing to the incidence of cancer of the breast and of the uterus.

The mode of metastasis of cancers is by the lymphatic vessels, either by direct extension, as emphasized by Handley in reference to the breast, or by embolism. Certain cancers, however, grow in intimate relation with blood vessels, as certain thyroid cancers and chorionepithelioma; these are more likely

to metastasize by the blood stream, the emboli lodging first in the lungs and there setting up secondary growths. The transformation of benign to malignant epithelial tumors is generally regarded as possible in spite of the lack of convincing evidence. A cancer usually follows the type of epithelium from which it originates, and the same rule holds true when it is derived from a pre-existing benign tumor.

The epithelial cells may undergo mucinous, colloid, hyaline and fatty degeneration, calcification and necrosis. As the result of fatty degeneration, especially when associated with necrosis, a more or less viscid, opaque, granular fluid can be scraped from the cut surface, the "cancer milk." The connective tissue often shows mucoid or hyaline degeneration. Uninfected cancers show much marginal reaction in the form of cellular infiltrates of lymphoid, endothelial and plasma cells.



FIG. 172.—Epidermoid cancer, squamous epithelioma, show nest of cells, differentiation and pearl formation.

As compared with the sarcoma, the carcinoma shows no capsule, is less vascular, less subject to hemorrhage, more subject to necrosis; its metastases are characteristically by the lymph stream and therefore tend to be regional rather than widespread.

Epidermoid Carcinoma. Epithelioma.—The epidermoid cancers originate in areas covered by stratified squamous and transitional epithelium. The tumors may occur as ulcers, as nodules or as papillary masses. Striking examples are found in the lip, tongue, esophagus, anus, and in the skin surfaces, more particularly of exposed parts. It is often possible to see in a given section, transi-

tions from normal surface epithelium to true tumor growth. The deeper interpapillary epithelium is first seen to be growing deeply into the corium; solid masses of cells are formed, from which branching columns penetrate more deeply and extend into the deeper parts. The extension is in three diameters, so that a single section may cut numerous strands more or less transversely, thus giving the appearance of isolated islands of cells. It is true that isolated islands may be formed as the tumor extends through lymphatics and tissue spaces (lines of least resistance), but in the primary tumor most of the cell masses are interconnected. The growth tends to form layers of basal, intermediate and squamous cells. In the cutaneous cancers and in certain of those originating from transitional epithelium, keratinization is well marked. The keratinization is central in the mass, i.e., away from the peripheral basal cells, and thus the flat horny cells are deposited in concentrically laminated cell whorls or epithelial "pearls." When the tumor contains many such "pearls" it

is often called a cancrroid, a term which indicates a relatively low grade of malignancy. Hyaline inclusions in the cells are not uncommon and cell bridges are often well displayed. On the other hand, epidermoid cancers may show no "pearl" formation and relatively little keratinization. The cells show the usual characters of stratified squamous epithelium. The intermediate cells and to a less extent the basal cells may show chromatic disturbances of nuclei. Mitotic figures are not more frequent in the basal than in the intermediate cells, but are likely to be multipolar and atypical. Many of these tumors originate as ulcers or become ulcerated, and inflammation of acute or chronic forms is common. In certain situations, as the cervix uteri, the cellular infiltrate may be made up largely of eosinophiles. Necrosis may or may not be extensive. In the cervix uteri and sometimes in other situations, there may be much central necrosis of the cell masses instead of keratinization. In various situa-

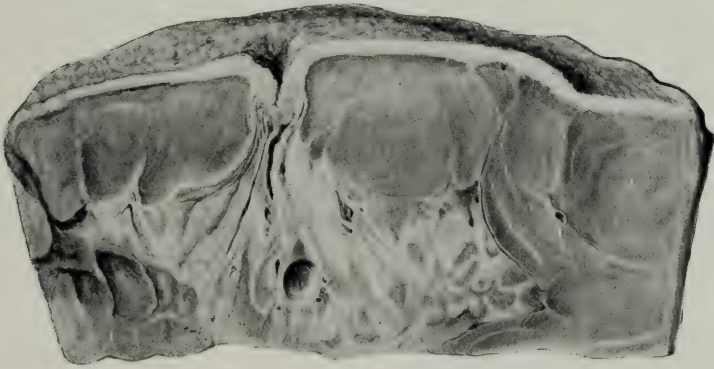


FIG. 173—Scirrhus carcinoma of breast, showing retraction of surrounding structures, notably the nipple, dense character of tumor and cyst formation.

tions the "pearls" may become necrotic; they may also serve as bodies around which foreign body giant cells form.

The basal cell epithelioma is most common in the exposed skin of old people, especially angles of eyes, nose, ears and upper half of face, but may occur in other situations, notably as "rodent ulcer" of the foot or other skin areas, and may constitute a part of congenital mixed tumors. Superficial basal cell epitheliomata are usually chronic ulcers, not subject to the more severe forms of inflammation, beginning insidiously, progressing and eroding very slowly. Histologically, they are made up of relatively small, uniform cells of about the size of the basal cells of epiderm, are round, cuboidal or polyhedral. The cytoplasm is rather basophilic than acidophilic, the nuclei small and relatively dense, mitotic figures present but not frequent. Invasion is observed but is not marked. Degenerations and secondary inflammatory changes are much the same as in the squamous epithelioma. A confusing condition in the skin is the so-called benign cystic epithelioma or acanthoma adenoides cysticum, which appears grossly as a small nodule, usually ulcerated, and histologically is found to be sharply circumscribed, lobulated and made up of the

basal type of cell; often the center of the cell masses or lobules show small cyst-like spaces.

Epidermoid cancers as a rule are not extremely malignant as compared with other forms of malignant tumors. Those with many "pearls" are supposed to be the least malignant. The basal cell forms in old people often exist for many years without metastasis. If treated early, recurrence may be avoided. Delay or improper treatment, however, increases the chance of recurrence and the possibility of metastasis.

Cylindrical Cell Carcinoma.—This general group of cancers may be derived from surface epithelium of cylindrical type or from duct and gland epithelium. It may appear grossly as of scirrhus, medullary or mucinous type. Histologically, there are two principle forms, the carcinoma simplex and the adenocarcinoma. Both the scirrhus and medullary form may be histologically simple or glandular in character; the mucinous form, often incorrectly called colloid carcinoma, is usually of glandular type.

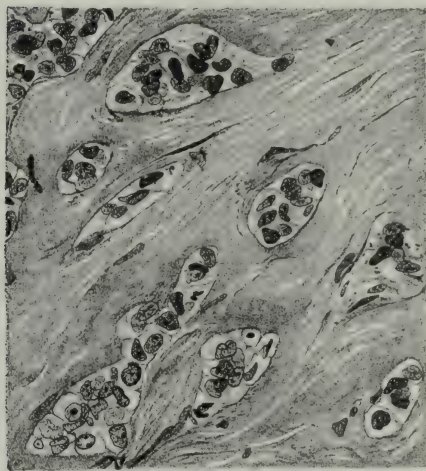


FIG. 174—Scirrhus carcinoma of the simplex type.

Carcinoma Simplex.—The carcinoma simplex is diagnosed by its microscopical appearance. It occurs in glandular organs and in tissues covered by columnar epithelium. The cells of the tumor are arranged in solid masses, nests and cords, supported by variable amounts of connective tissue. Marginal areas often show very clearly the extension through lymphatics. The individual epithelial cells are no longer cylindrical, but are spheroidal or polyhedral with moderately acidophilic, finely granular cytoplasm

and occasional cell inclusions. The nuclei are vesicular and occupy a fairly large area of the cell; normal and abnormal mitotic figures are present and sometimes multinucleated cells are seen. There is practically no intercellular reticulum. The cells are irregularly placed, and no arrangement of marginal basal cells or formation of acini can be discovered. Fatty and other types of degeneration occur, and it is not uncommon to find necrosis in the center of cell masses or involving a large part of the tumor. In the scirrhus varieties the connective tissue is rich and in the medullary forms poor. In either case, it is usually poor in cells and rich in collagenous fibers. The scirrhus is usually densely fibrous and the connective tissue often hyalinized. The epithelium is present as narrow cords or bands of cells, and the cells are often smaller than their normal prototype. A scirrhus may at any time become cellular and grow rapidly, but the integral part the connective tissue plays is shown by the fact that often the metastases are quite as fibrous as the original tumor. The connective tissue of the scirrhus tends to contract so as to produce a slowly growing, dense

mass with little necrosis, moderately invasive, firmly adherent to and producing retraction of the surrounding parts. Such tumors cut with leathery resistance and show a dense retracting, pearly gray cut surface, often showing small yellow areas of epithelial masses. Metastasis is usually late and scanty. The medullary cancers grow more rapidly, invade deeply, metastasize early and widely. They are massive, ill defined, soft tumors which cut with ease showing a soft bulging, moist, necrotic or hemorrhagic cut surface. The knife will scrape from the cut surface a viscid, granular, cloudy yellow fluid, "cancer



FIG. 175—Adenocarcinoma of the pylorus, showing hyperplastic glands and deep situation of acinus-like cancer nests.

juice or milk," made up of liquefied cells and tissues. Although a scirrhus may become softer and even of medullary type, the reverse is not observed. Reactive inflammation with infiltration of mononuclear cells is common. In certain situations, particularly in the alimentary canal, histo-eosinophilia occurs.

Adenocarcinoma.—Borst would limit this term to adenomata which show cancerous change, and use the term carcinoma adenomatosum for the cancers with disposition to form gland-like acini. Nevertheless, the term adenocarcinoma is generally used in English and American literature to include all varieties of acinus forming cancers. Such tumors may originate in any variety of cylindrical epithelium. Grossly, they have no distinguishing

features unless cysts are formed; otherwise they do not differ from the carcinoma simplex, except that the latter is more often a scirrhous than is the adenocarcinoma. The cells are more highly differentiated in that they are arranged with a tendency to form more or less characteristic acini. Tumors occur which are generally of the simplex form, but which here and there show small acini; if this can be made out clearly they are referred to as adenocarcinoma. On the other hand, acinus formation may be very prominent. The acini are of irregular outline and size, cell lining tends to be multiple, with a disposition to fill the acinus. Solid columns of cells extend from the acini through tissue spaces. Basement membrane is incomplete or often absent. The cells are like simple or stratified columnar epithelium. Mitotic figures are



FIG. 176—Adenocarcinoma of the breast.

frequent, often abnormal and multipolar, and with lack of uniformity in equatorial plane. Arising from places where ciliated epithelium exists, the tumor cells may be ciliated. Cancers of the rectum are particularly likely to show mucinous goblet cells. Papilla formation may be extensive within the acini, giving rise to the name papilliferous adenocarcinoma. Necrosis is common, reactive inflammation almost constant, and acute inflammation resulting from erosion frequent.

Cyst formation in adenocarcinoma is by no means rare, the cysts containing papillary outgrowths or various kinds of fluid. Cancers of the colon are especially prone to the formation of multiple cysts filled with mucin. These are often called colloid cancers because of the brown color and gelatinous consistence of the mucin. It is obvious that the correct term is mucinous carcinoma. Grossly, such tumors are poorly defined, of variable size, and of relatively soft elastic consistence. They cut with ease and show a soft, friable,

gelatinous cut surface either with little tissue definition, or of cystic character, the loculi measuring a few millimeters in diameter, and containing viscid or semisolid mucin. Microscopically, the picture is fundamentally that of adenocarcinoma, differing in that the acini are filled and more or less distended with hyalin or granular basophilic mucin. It is unusual to find much mucin within the cells. Distention may flatten the lining cells. Desquamation of more or less degenerate cells is common, and the picture of a small cystic space filled with mucin, with few or no lining cells, and with centrally disposed, clumped, desquamated cells in the mass of mucin, is common.



FIG. 177—Mucinous carcinoma of the colon, showing acini with desquamated cells and masses of mucin in acinus-like structures free from cells.

Regression of cancer may occur as the result of radiation or spontaneously. The tumor cells undergo degeneration and necrosis and a diffuse growth of connective tissue occurs. Radiation produces rapid necrosis of cells with pyknosis, karyorrhexis and karyolysis (see Loeb). Tumor cells may become multinucleated. Sometimes phagocytosis of destroyed cells is observed and in more extensive destruction, especially as the result of thrombosis of vessels, foreign body giant cells are found. The changes in spontaneous retrogression are slower and less pronounced. Fibrosis proceeds from the margins and is essentially organization and cicatrization. Such appearances are quite different from those of the scirrhus cancer, which shows large bands of connective tissue and is a progressive lesion.

SPECIAL EPITHELIAL TUMORS

Introduction.—In this group are placed certain tumors whose cell character does not correspond to ordinary adult epithelium. They are therefore difficult to classify with the groups of tumors as given in our outline. In each instance, however, the cells from which they arise originate in embryonal epithelium. The same is true of tumors of the nervous system, but in this instance the tumors show cell types in more or less close resemblance to adult cells, not of mature epithelial character.

Chorionepithelioma.—This tumor is derived from the covering cells of the chorionic villi. The cells which take part in the tumor growth are the cuboidal cells of Langhans and the syncytium, both of which are derived from trophoblast and thus genetically similar to ectoblastic epithelium. The tumor usually develops several months after delivery of a hydatidiform mole, abortion, miscarriage or normal pregnancy, but may occur earlier. It may arise from residual chorionic villi in the placental site or from villi or villus cells which become lodged in uterine veins. Rarely villus cells may be transported to neighboring veins as those of the vagina, and set up tumor growth there. Chorionepithelioma may even appear as part of teratoid tumors in the testis. The common variety of the tumor appears as a soft, red, spongy, often hemorrhagic tumor projecting into the cavity of the fundus uteri. Cross section shows definite penetration of the mass into the uterine wall. Histologically, it shows irregular masses of cuboidal cells, with small vesicular or solid nuclei and finely granular or somewhat vesicular edematous cytoplasm containing glycogen; intermingled are multinucleated cell masses representing the chorionic syncytium. The cytoplasm of the multinucleated cell masses is usually vesicular and may contain much fat; the nuclei are usually dense rather than vesicular. Mitotic figures are more common in the cuboidal than in the multinucleated cells. The blood vessels are numerous and often cavernous; in the latter, masses of tumor cells are often found. Uterine curettings may contain retained placenta, which histologically shows masses of cells similar to those of the chorionepithelioma. The diagnosis in these cases is simply retained placenta, unless there is great irregularity of cell growth with fairly rich vascularization, or definite penetration of muscularis. The intravascular position of much of the chorionepithelioma determines local extension to neighboring parts, particularly the vagina, and metastasis through the blood stream, most often to the lungs, rarely to the heart or other viscera.

The chorionepithelioma or choriocarcinoma is to be distinguished from the malignant hydatidiform mole or chorio-adenoma. The latter represents the invasive stage of the mole wherein, with preservation of the connective tissue part of enlarged and multiple cystic villi, the epithelium proliferates extensively and invades the uterine sinuses and musculature. Destruction and penetration of the uterus may occur but metastasis is rare.

Adamantinoma.—The adamantinoma is a tumor originating in enamel organ, or in remnants in the jaw of epithelium which has been displaced from the dental groove. They are more common in the lower than in the upper

jaw, invade the jaw and may attain very large size. They are locally invasive, may recur after removal but rarely show distant metastases. They may be of bony hardness or of less firm consistency, and may be solid, spongy or cystic. The solid and more malignant forms are commoner in the upper jaw, while the cystic forms are more frequent in the lower jaw. Histologically, they are cellular tumors characterized by the presence of enameloblasts. These form the margins of cell masses which centrally show several types of differentiation. In some tumors the central cells may be flat, keratinized epithelium with intermediate prickle cells. In others, the central cells are cuboidal or spindle

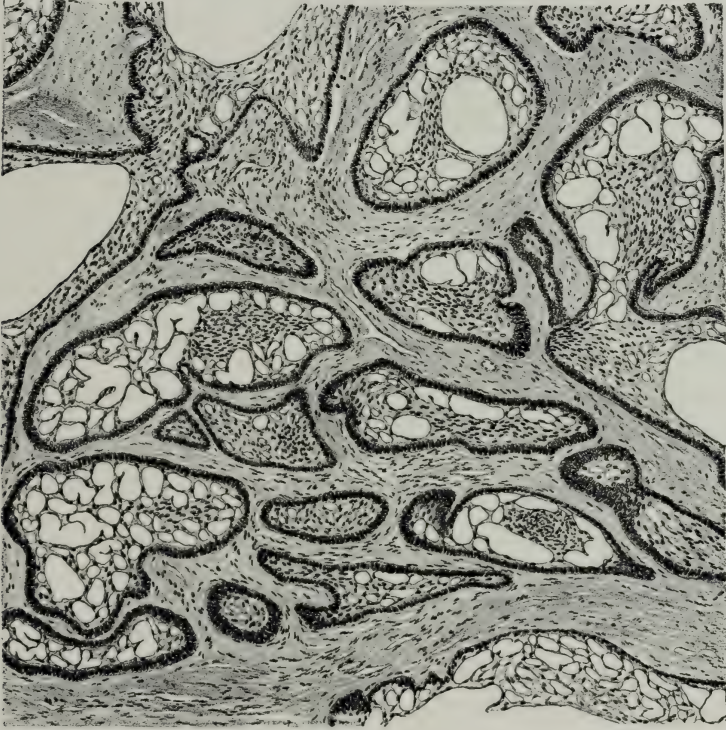


FIG. 178—Cystic type of adamantinoma.

form. Most frequent, in our experience, are those forms in which the enameloblasts form acinus-like structures filled with a granular fluid, the columnar enameloblastic cells differentiating to form spindle or stellate cells toward the lumen. The connective tissue is variable in amount, is not well vascularized, may show hyaline or mucoid degeneration and occasionally appears sarcomatous. These adenomatous forms are responsible for the grossly cystic tumors.

Hypernephroma.—In the generally accepted nomenclature of tumors the use of an organ name as a prefix is not permitted, the tumors being named on the basis of histology rather than organology. The term hypernephroma, referring to a tumor composed of cells of adrenal cortex, is in good usage and is an exception. The term adrenal carcinoma, genetically more correct is misleading in that it gives the impression that the tumor is in the adrenal gland,

whereas it rarely occurs in that situation. According to Keibel and Mall, quoting Soulie, the suprarenal cortex is derived from celomic epithelium. Its primary situation near the developing urogenital tract, is apparently responsible for the fact that aberrant and accessory suprarenal substance may be found almost anywhere in the adult urogenital tract, as well as in liver and pancreas. Adrenal inclusions in the renal cortex (choristoma) are common. Here they may remain quiescent throughout life, or become the point of origin of tumors with malignant characters. Similar inclusions elsewhere may give rise to the same type of tumor. Hypernephroma occurs most often in the kidney, and is the commonest tumor of the adult kidney. Although small, benign, circumscribed adenomata are common in the adrenal, the hypernephroma is rare; primary tumors of any considerable size are usually derived from the medulla. Adrenal inclusions in the renal cortex are usually small, circumscribed, pale yellow masses, usually in the upper pole, which histologically form a somewhat irregular, corded mass of large, square or polygonal mononuclear cells with vacuolated cytoplasm. The hypernephroma also originates in the upper pole and grows in part by compression and in part by invasion of the kidney. Grossly, they are tumors several centimeters in diameter, well defined, moderately invasive, usually solid but sometimes cystic, softer than kidney and of yellow color; they cut easily and show a soft, yellow, well vascularized and often hemorrhagic cut surface. Histologically, the type

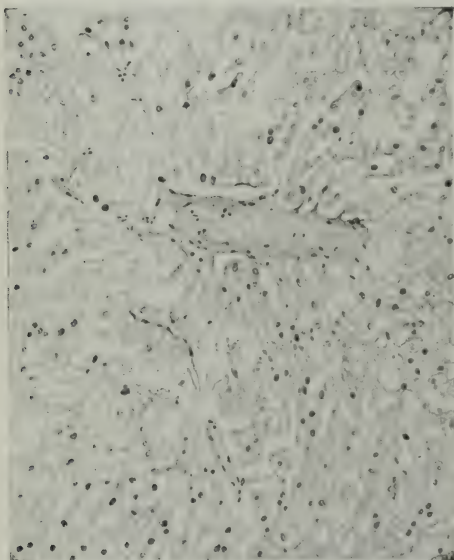


FIG. 179—A hypernephroma showing the columnar arrangement of the large vacuolated cells with a vascularized trabecula.

cell is like that of adrenal cortex, large, round, square or polygonal, with vesicular cytoplasm and small vesicular nuclei; mitotic figures are variable but usually not frequent. These cells are supported upon, and appear to grow from, ramifying vascularized connective tissue septa. Cell cords and even arrangements suggesting tubules may be found. Necrosis and hemorrhage are common. The production of epinephrin is doubtful, as would be expected in a tumor made up principally, if not entirely of cortical cells. The chemical content of fats and lipoids, as pointed out by Wells, and the staining reactions for glycogen show a close similarity to cells of adrenal cortex. Hypernephromata extend by infiltration of kidney and then of the renal veins. Tumor thrombosis may extend along the renal vein and inferior cava as far as the heart, sometimes producing obstruction of the inferior cava and its tributaries. Emboli may break off at any time and produce metastases in the lungs.

Since the description of hypernephroma by Grawitz in 1883, numerous workers have pointed out the possibility of confusing renal cancers with hypernephroma. The cells of hypernephroma may be non-vesicular and may be columnar or flattened in growth. Renal cancers may be of carcinoma simplex type, adeno- or tubular adenocarcinomatous type, or papilliferous; they may originate in preëxisting adenomata, areas of abnormal development, probably in retention cysts, and appear as a part of congenital mixed tumors. The more distinctive types are characteristic, but aberrations in the cells of hypernephroma and the assumption of vesicular cytoplasm by cells of papilliferous and other cancers, serve to inject much confusion into diagnosis, which all too often must be a matter of opinion. Grossly, the cancer is more likely to be of pale, fleshy character than is the hypernephroma, but we have observed one cancer of the kidney in which yellow necrotic areas appeared much as in hypernephroma.

MIXED TUMORS

Introduction.—Mixed tumors include a wide variety of tumors, which do not conform to those already considered, in that they contain several tissue or cell types instead of only one main tumorous element. There may be mixtures of several different connective tissues, or of connective tissues and epithelial structures, in which the connective tissue plays a greater part than that of support, or there may be representatives of practically all the tissues of the body. Some of these have been mentioned in the foregoing discussions but have not been classified. These tumors, then, represent adult tissues of types which take origin in one, two or three germinal layers of the embryo, and may be classified as mono-, bi-, and tridermal mixed tumors. We prefer, however, a simpler classification in which those representing one or two layers are called mixed tumors and those representing all three layers are called teratoid tumors or teratomata. It is of interest to speculate as to whether these tumors originate in single cells or cell groups of blastoderm or original embryonal layers, or arise from cells in which varying degrees of differentiation have occurred. If the first supposition be true, the simpler mixed tumors are the derivatives of multipotential cells. In so far as concerns these tumors the problem has not been solved, but in the teratomata, the common situation in sex glands would make it seem probable that aberrations in germinal cells may lead, by development from totipotent cells, to the multiple tissues in the tumors. As has been indicated earlier, there is little experimental evidence relating to the question. Mixed tumors vary considerably as to recurrence and metastasis and in this relation only the individual tumor types can be discussed. Malignancy may develop in mixed tumors that are primarily benign. If this occur, the metastases may be made up of only one or two elements, or all of the constituents, of the primary tumor. Rarely, a primary malignant tumor may be mixed to form a combined carcinoma and sarcoma, a point to be discussed subsequently. The field of mixed tumors is so large and individual cases show such great variations, that it is possible only to indicate some of the more important features.

Mixed Tumors.—Arbitrarily we include here those tumors composed of tissues representing derivatives of only one or two embryonal layers. These comprise tumors already described, as for example, such simple mixtures as osteochondroma and more complex forms as the fibromyxolipoma or liposarcoma. Two forms of the mixed tumor, the mixed tumors of salivary glands (especially parotid) and embryonal mixed tumors of the kidney, deserve special consideration.

Mixed Tumors of Salivary Glands.—This type of tumor may occur in any of the salivary glands, the gums and in certain other situations (author has observed one in the orbit), but are most common in the parotid gland. They occur in adult life, usually grow slowly as firm, in the early stages movable, sometimes nodular, tumors, varying in size from the usual diameters of one or two centimeters to very large size. As they enlarge they become increasingly adherent to surrounding structures.

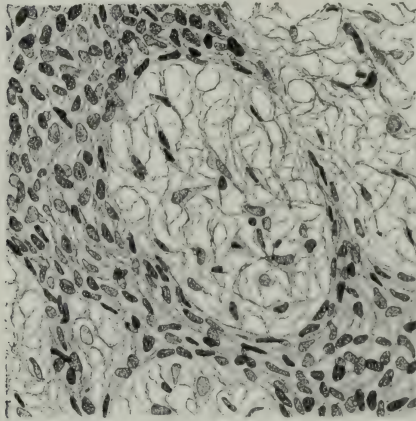


FIG. 180.—Small section of a mixed tumor of the parotid gland with epithelial type cells and mucoid tissue.

When excised they are fairly well circumscribed but as a rule, only partly if at all encapsulated. They are firm, pale, and often resemble chronically enlarged lymph nodes; they cut with considerable resistance and show a slightly bulging, moist, pale cut surface usually free from necrosis. Microscopically, there are several elements present, all but one of which can be regarded as mesoblastic. A ground substance of connective tissue may show fibromatous, myxomatous, chondromatous and sometimes other elements. Supported on this are numbers of round cells of moderate size, with moderately chromatic nuclei and fairly

dense cytoplasm. Mitotic figures are rare. These cells may be simply in masses, or may be arranged to form acinus-like structures, which may contain mucin or mucoid; they may also be arranged to form tubular spaces containing hyaline cylinders, thus exhibiting cylindromatous character. Numerous studies have been carried out to determine the nature of these cells and the origin of the tumors. The view that the cells are endothelial and give rise to the other elements of the tumor, is not supported by more recent studies which have pointed out the occasional appearance of cell bridges and of "pearl" formation. The relation of the parotid anlage to branchial clefts makes it possible that the tumor arises from embryonal inclusions, a hypothesis that cannot be rejected. Ewing in an extensive discussion of the subject, points out that certain adenomatous mixed tumors arise from gland acini and ducts, and that others probably arise from branchial inclusions, but that most of them originate from gland epithelium, which "as has been satisfactorily proven," may give rise to mucous tissue and cartilage. Removal of the encapsulated forms is usually successful,

but removal of the partly or unencapsulated forms may be followed by repeated recurrence and malignant change may ultimately occur.

Embryonal Mixed Tumors of the Kidney.—These tumors are fairly common, usually appear in the first three years of life and may attain enormous size, diameters of thirty-five, thirty-seven and forty centimeters having been reported. They are almost always intrarenal but may be entirely extrarenal. They are large, fairly dense, usually encapsulated, smooth or lobulated tumors, sometimes with large single or smaller multiple cysts. Upon section, the cut surface is usually fleshy, bulging, moderately vascularized and may show necrosis and hemorrhage. Microscopically, the picture varies in different

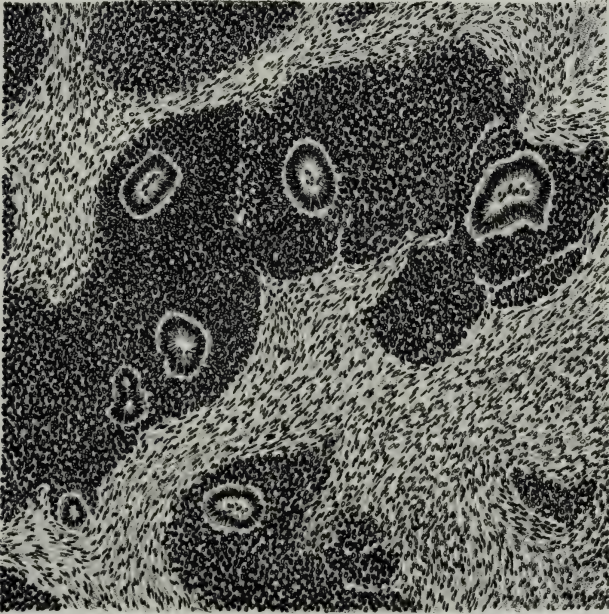


FIG. 181—Embryonal mixed tumor of the kidney with spindle cells, round cells and tubular structures.

parts of the tumor. The most constant feature is the presence of medium sized round or oval cells with fairly dense cytoplasm, frequently containing glycogen, and a small, slightly vesicular nucleus. These fuse with areas of spindle cells, which in some tumors predominate. In the cellular masses are acinar or tubular areas, surrounded by cuboidal or cylindrical cells, which may be separate from or fused with the surrounding less differentiated cells. The spindle cells often show the characters of sarcoma. Intermingled in the tumor are areas of other types of tissue, not all of which are necessarily present in each tumor, namely cartilage, smooth muscle, embryonal striated muscle, fat, edematous and myxomatous connective tissue, and rarely other types of tissue. It seems probable that these tumors originate in renal blastema, the cells differentiating to form the various tissues and cells of the tumor. Although the histological picture is often characteristic of malignancy, metastasis

is rare; when it occurs it is most common in the liver, but may appear in lungs and other organs.

Mixed Carcinoma and Sarcoma.—Occasionally, malignant tumors arise in which it appears that carcinoma and sarcoma are combined. The arrangement is in the form of masses of the different types of cells, rather than an intimate intermingling of the two. The usual combination is carcinoma simplex and spindle cell sarcoma. Experimental studies throw little light on the phenomenon, because of difficulties of interpretation. For example, the transformation of a carcinoma, in about the thirty-fifth generation of transplants, into a tumor morphologically a sarcoma, is variously interpreted as either a true transformation or as a metaplasia of epithelial cells, the mass of opinion being in favor of transformation. The interpretation of non-experimental tumors meets the same difficulty. The spindle cell masses associated with a carcinoma simplex may be spindle shaped forms of epithelial cells and the question is not solved by naming these tumors sarcomatoid carcinomata. Nevertheless, it seems certain that the two tumors may occur coincidentally. It is possible that carcinoma and sarcoma may originate in neighboring points and grow as a combined tumor or "collision" tumor. The two types may originate in one focus, or the stroma of a carcinoma may undergo sarcomatous change. The third possibility, which probably applies to many of these tumors and mentioned above, is that epithelial tumor cells may show in one part typical carcinoma and in other parts spindle cells of epithelial character. Before final diagnosis, granulation tissue must be carefully excluded. The separate metastasis of both forms would aid materially in establishing the diagnosis in a given case.

Teratomata.—The teratomata include certain blastomatous tumors and progressively growing tumor-like embryonal inclusions, in which representatives of all three embryonal layers are present in disorderly fashion. The latter group shades into the group of monsters, but monsters are characterized by a more orderly arrangement of tissues and organs. On the other hand, in their undeveloped forms they represent the condition spoken of earlier as hamartoma. The blastomatous tumors of teratoid nature contain immature cell forms and are often malignant. The fetal inclusions show mature cells, tissues and organoid forms. They differ from the monsters not only in the disorderly arrangement of tissues, but also in that their individual tissues are prone to true blastomatous proliferation and malignancy. It can readily be seen that with all three layers of the embryo partaking in the production of the tumors and tumor-like masses, the possible combinations are almost innumerable. Fundamentals of classification may serve as a guide in individual tumors, but only a few of the more common varieties can be discussed. As has been indicated, the teratomata may be classified as immature forms with relatively undifferentiated cells and tissues, which are younger than those of the host, or as adult coetaneous forms in which the cells and tissues are mature and of the same relative age (either from the point of view of actual age—fetal inclusions—or that of differentiation) as the host. Since many of the tumors

arise in sex glands, the classification into genital and extragenital varieties is of importance.

Teratoma of Testis.—This tumor is fairly common in the adult testis, and is said to be more frequent in undescended than descended testes. The mature type of teratoma shows histologically a variety of cells and tissues, such as connective tissue, mucoid tissue, cartilage, bone, epithelium of almost any variety, glands, gastric mucosa, various components of the nervous system,

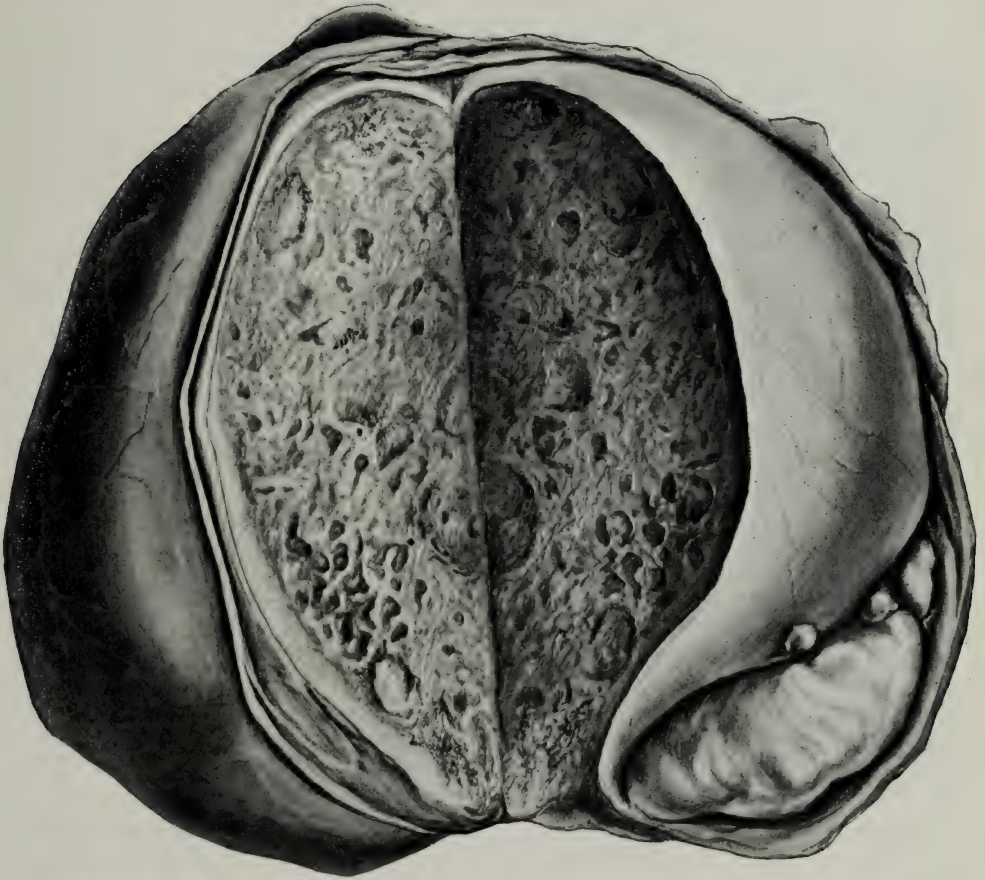


FIG. 182—Teratoid tumor of the testis, exact size, showing variable character of cut surface.

etc. Malignant changes in any of the elements of the tumor may be observed and the metastases may be carcinoma, sarcoma, or represent several elements of the original tumor. Grossly, the tumor may attain considerable size, but is usually observed and removed fairly early in its course. Circumscribed, often encapsulated, it may grow within the testis destroying it or may push it aside. It is a bulky, usually nodular tumor, and although sometimes cystic rarely shows the dermoid cysts so common in the ovary. A less differentiated form is exemplified in the rather unusual chorionepithelioma of the testis. A third form, relatively common, is immature and made up of undifferentiated cells.

Grossly, these are likely to be large, soft, vascular, fleshy or mottled masses, often with extensive necrosis and hemorrhage, and distinctly invasive. Microscopically, they are made up of large polyhedral or round cells in masses of discrete cells rather than in sheets. They are commonly alveolated, resembling the large round cell sarcoma, but may show no alveolation. By comparative studies, these have been demonstrated to be embryonal cells with totipotential characters. Morphologically, they are to be regarded as immature genital teratomata. These tumors may be either a one-sided development of a more

mature type of teratoma or may be purely an immature form. It is possible, however, that some of them may be cancers originating in spermatoblasts. Metastasis is common and the secondary nodules may give a picture resembling lymphosarcoma.

Ovarian Teratoma.—

The teratoid tumors of the ovary may be solid or cystic. The solid forms are rare, are unilateral, and both grossly and microscopically resemble the mature and partly mature forms described in the testis. The cystic forms, much more common, are the so-called dermoid cysts, or more specifically complex dermoid cysts.

Complex Dermoid Cysts.

—These are mature forms

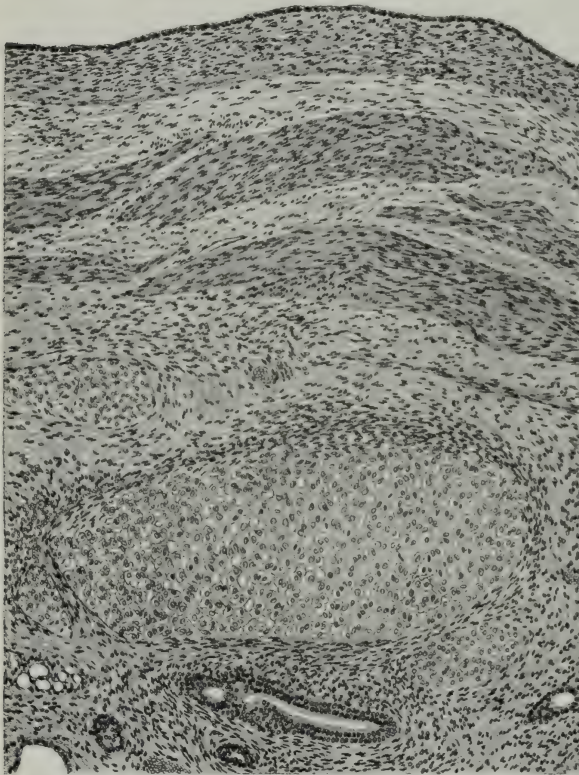


FIG. 183—Teratoid tumor of ovary showing smooth muscle, connective tissue, cartilage and gland structures.

of teratoma and are properly called cystic teratomata. They may occur at any time of life but are most frequently encountered in middle age. They may be unilateral, bilateral, single or multiple, and may vary markedly in size. The common, large monolocular cyst usually shows a capsule and a moderately thick wall, which often at one point shows extra thickness. Upon opening the cyst a semifluid, oily or buttery, pale yellow or white, grumous mass is found, containing long interlacing hairs, which usually grow from the thickest part of the cyst wall. Microscopically, the wall shows a lining of skin with epiderm, papillary corium, sweat and sebaceous glands and hair follicles. The deeper parts of the wall show mature tissues and organoid forms, the total of which in various tumors includes practically all the tissues of the body except the

sex glands. Cartilage, bone, teeth, various epithelial structures, ganglion cells, neuroglia, etc., are common but organs such as liver, kidneys, pancreas are rarely present. Malignant change is not common. Similar tumors may occur in other situations, more particularly in body fissures and in the region of the branchial clefts of the neck.

The cystic teratoma must be distinguished from the simple dermoid, which may occur in a variety of situations, as a result of trauma or faulty development, the cysts containing grumous, buttery material and lined with skin but without mixed elements in the surrounding tissues. Epidermoid cysts may be of the same origin, but are surrounded only by epiderm instead of skin. Obstruction of sebaceous glands, rarely of sweat glands, produces cysts which often project on the skin surface and contain sebaceous material; the names often applied are atheroma cutis or atheromatous cysts of the skin, or sebaceous cysts.

Sacral Teratoma.—This condition, by no means common, is much more a fault of development (of the body fissures) than a true tumor. It appears as a nodular mass projecting from the region of the sacrum and coccyx, sometimes displacing the rectum anteriorly. Upon section it is usually spongy or cystic. It differs from the teratomata considered previously in that the tissues and organs composing it are much more mature. Rudimentary extremities, legs, arms, toes, fingers, may rarely be formed. Malignant change may involve any element.

Epignathus.—This projects forward from the pharynx, and may either be a complex teratoid mass with organs and organoid forms resembling the sacral teratoma or be much more mature, showing fairly well developed organs and parts of extremities. The latter variety might with justice be classified with the monsters rather than with teratomata. True teratomata and dermoids also occur in the pharynx.

Monsters.—In the development of the embryo and fetus a variety of conditions may determine abnormalities. These may be of little functional import and not incompatible with apparently normal life, or more severe and lead to shortened life, or so marked as to lead to intrauterine or early post-natal death. Some of the minor abnormalities, such as extra fingers and toes, are hereditary, but most others have no such basis. Only the more severe abnormalities are included in the term monsters. These may affect single individuals or be double monsters. In single individuals, the important monstrosities are connected with faulty development of the various body fissures, particularly facial (cleft-palate, harelip), branchial, urogenital and neural. In the last group are included cranioschisis and acrania due to faults near the cephalic pole, rhachischisis along the area of the spinal canal, and spina bifida at the caudal pole. The double monsters may be symmetrical or asymmetrical. The former include twin fetuses joined together at the cephalic poles (craniopagus), at the thoracic portion (thoracopagus), or at the caudal poles (ischiopagus). These may appear in extremely varied patterns. The asymmetrical

forms include numerous types of parasitic fetus attached to various parts of the body or included within the body. This group shades into the epignathi and sacral teratomata. Monster formation must be regarded as a pathological alteration of development of ovum and embryo, and the discussion of the etiology is therefore far reaching. The complete discussion of the forms of monsters is a catalogue of descriptive terms, and cannot be included in a book of this scope. The reader is referred to such works as those of Ballantyne, Hirst and Piersol, and most particularly Schwalbe, for details of etiology and morphology.

APPENDIX

CYSTS

Introduction.—The cyst is a sac with connective tissue or other type of wall, containing material different from that of the wall and usually either fluid or semifluid. Many cysts have no relation whatever to tumors and are included here simply for convenience; many tumors, however, contain cysts and even to such an extent as to be called cystic tumors; certain cysts by proliferation of elements in their walls may give rise to tumors. Cysts may be monolocular with only one sac, or multilocular with several sacs. They vary considerably in origin and may be classified as congenital or acquired. Our discussion is necessarily much restricted, but will be further developed in the sections of the special pathology of various organs.

Congenital Cysts.—These may be due to persistence of ducts established in embryonal life, which normally disappear, or to faulty development of glandular organs. Persistent tubes or ducts, which normally should completely disappear, may show interrupted closure because of disappearance only of parts; secretory or other products, may then accumulate and the tube remnant become cystic. Included in these are thyrolingual cysts in the midline of the neck, branchiogenic cysts in the region of the branchial clefts (often lined with ciliated epithelium and prone to form cancer) vitello-intestinal cysts near the umbilicus and urachal cysts in the lower abdominal cavity. Numerous types of cyst are found in relation to both male and female genital organs, due to persistence of remains of the Wolffian body, paroöphoron, Gaertner's duct, Muellerian duct, etc. Congenital cysts of glandular organs are best exemplified in congenital cystic kidney and liver. The congenital cystic kidney is usually considerably enlarged, made up of multiple cysts of diameters of a few millimeters to a centimeter or more, thin walled, containing colorless or pale yellow fluid, or colorless, yellow or brown hyaline material. The cysts of the liver are multiple, of moderate size, usually contain clear, colorless fluid and often appear to be dilatations of lymphatics. Adami mentions a so-called cystic diathesis in which both kidneys and liver are cystic, and in one of his cases the pancreas also.

Acquired Glandular Cysts.—These develop in preëxisting glands or ducts. There are two forms, the retention cyst and the follicular cyst. The retention cyst occurs as the result of occlusion of a duct or ducts. The corresponding

dilatation behind the obstruction may be temporary, if the obstruction be removable, or permanent. If temporary, the subsequent changes in the gland depend upon duration. In a general way obstruction leads to atrophy and disappearance of the parenchymatous cells, with a more or less successful attempt at replacement fibrosis. It is of interest that in the pancreas the islets of Langerhans survive long after the disappearance of the acinar cells. It is of further interest that the secretory pressure in glands may be so great as to produce large cysts, the contents of which, more or less different from the normal secretion, may be under extremely high physical pressure. This pressure probably induces an inflammatory fibrosis in addition to replacement fibrosis. Retention cysts occur in the skin glands, especially the sebaceous cyst, in salivary glands ("ranula" of sublingual glands), pancreas, kidney, liver and other organs. Similar cyst accumulations occur in the gall bladder, chronically inflamed Fallopian tubes, etc. Follicular cysts occur in glands without ducts and are well represented in the thyroid and ovary.

Cysts in Solid Organs.—These are due to necrosis and softening of localized areas. Anything which can produce localized necrosis may produce these cysts, the most common being vascular occlusion or hemorrhage. The best examples are in the brain, where an area of necrosis due to vascular occlusion undergoes liquefaction necrosis, and is surrounded by a fibrous and neuroglial capsule to produce a cyst. The same phenomenon may follow a hemorrhage, the cyst contents in this case being tinged brown by blood pigment, as are also the walls of the cyst. Ducts may rupture into solid organs, secretions accumulate, and become organized with the formation of cysts. Cysts of this general group are often called pseudocysts.

Parasitic Cysts.—Although small cysts may be formed by the fibrous tissue deposit around *trichinella spiralis* in muscle, the only large parasitic cyst in man is that of the *cysticercus* stage of *tenia echinococcus*. The adult form occurs in the dog, the feces of which contain the ova. Transferred to the intestinal canal of man, the *cysticercus* stage is built up in the liver or more rarely in other viscera. Usually one large cyst is formed containing fluid and daughter cysts. The major cyst has a wall made up of concentric hyaline laminae surrounded by fibrous tissue of the host. Fluid from the cyst usually contains hooklets from the scolices of the worm, but sterile cysts are sometimes encountered. Old cysts may contain only a pale brown or yellow gelatinous material. Occasionally, the daughter cysts project outward from the primary cyst to form a multiloculated cyst.

Neoplastic Cysts.—In the consideration of certain epithelial tumors, particularly of adenomatous character, it has been pointed out that distention may occur to form cysts, with or without papilla formation, and sometimes with special contents, as in the mucinous cancers. Tumors may also exhibit necrotic cysts or hemorrhagic cysts in much the same form as they occur in solid organs. The glioma is not infrequently cystic, probably due to necrosis, but in certain instances possibly of ependymal character.

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SYSTEMIC PATHOLOGY

CHAPTER XIII.

THE CARDIOVASCULAR SYSTEM

HEART.

PERICARDIUM.

ENDOCARDIUM.

MYOCARDIUM.

ARTERIES.

VEINS.

LYMPHATICS.

PERICARDIUM.

Congenital Abnormalities of the pericardium are unusual. The pericardium may be entirely absent in cases of ectopia cordis. Defective development of the pericardium may result in absence of part of the parietal layer, usually of the left side and anterior portions, so that the left lung and heart lie in a common cavity. Diverticula and failure of attachment to the central tendon of the diaphragm are also reported.

Degenerations of the pericardium occur usually as a part of inflammations. The only common infiltration is by fat, occurring in connection with obesity, of little practical significance and not to be confused with fat infiltration of the myocardium. Atrophy of subepicardial fat is common in long standing wasting diseases, and is often an associated condition in atrophies of the heart. The reduction in amount of fat is usually associated with an infiltration of fluid producing the so-called serous atrophy of fat. The fat in the heart grooves is of pale yellow color, soft and of translucent, gelatinous character, and the overlying epicardium flaccid and wrinkled.

Circulatory Disturbances are common. Active hyperemia appears as a part of inflammation. Passive hyperemia is usually the result of failure of the myocardium, but may also result from mediastinal tumors or inflammations, with pressure upon pericardial veins. The most important sequence is accumulation of edematous fluid within the sac, called *hydropericardium*, or hydrops pericardii. The fluid is of low specific gravity, poor in cells and does not clot in a mass, although small fibrin flakes sometimes form after withdrawal. The pericardium normally contains 20 to 50 cc. of clear, straw colored, limpid fluid, but arbitrarily hydropericardium is not diagnosed pathologically unless 100 cc. or more are present. It is not uncommon to find 400 or 500 c.c. of fluid, and amounts up to 2000 c.c. and more are reported. Williamson finds that fluid injected in the pericardium accumulates first along the diaphragmatic surface, pushing down the left lobe of the liver, then about the great vessels at the base of the heart; only when the fluid is large in amount is the anterior wall of the heart covered. The small amount of fluid normally in the pericardium exerts no pressure influence. When excesses are present in amounts sufficient to compress incoming veins, there is a decrease in arterial pressure and an in-

crease in venous pressure, due to damming back of blood from the lungs and reduced inflow into the left heart. Increased vasomotor tonus may maintain systemic pressure for a considerable period. Starling found that extremely slight increases in intrapericardial pressure (e.g. 2 or 3 mm. mercury) may cause a profound fall of systemic pressure. Lewis states that decreased intrapericardial pressure may elevate arterial pressure. Katz and Gauchat ascribe pulsus paradoxus to alteration of normal variations of intrapericardial pressure, when fluid is present in excess. In hydropericardium, the myocardium is usually at fault before the fluid accumulates and is further embarrassed by the pericardial pressure. With fluid exudates, the myocardium is usually the seat of degenerative changes incident to infections, and is further affected by the pressure of fluid. In hemopericardium from rupture of aneurysm or heart wall, the intraventricular or intra-aortic pressure is directly communicated to the pericardium, and far exceeds the attempt at compensation by increased muscular work and vasoconstriction, so that death rapidly ensues.

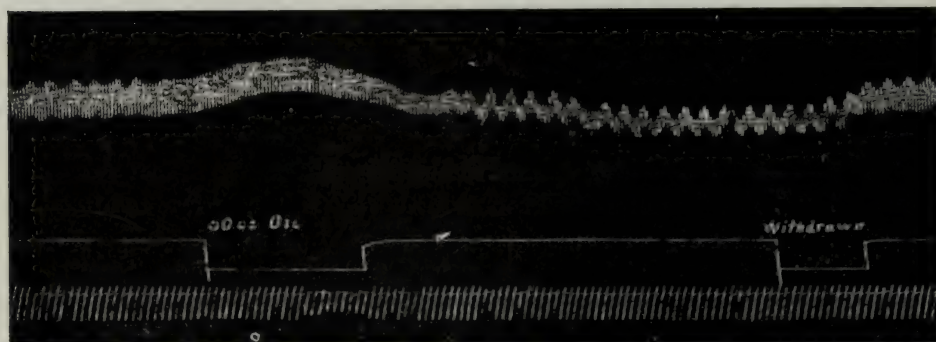


FIG. 184.—Tracing of blood and pulse pressure in experimental hydropericardium in the dog. The signal line is also the base line. Time in two seconds. Note after the primary rise the fall in mean arterial and pulse pressure following injection of 30 cc. olive oil into the sac, with restoration to normal upon withdrawal of fluid.

Hemorrhage into the tissues of the pericardium may appear as small petechiæ in death from asphyxia or convulsions, in tuberculous pericarditis, pericarditis due to hemolytic bacteria, tumor involvement of the pericardium and such hemorrhagic diseases as scurvy and purpura. In association with these conditions, the pericardial fluids may be more or less mixed with blood. *Hemopericardium*, indicating the presence of free and unmixed blood, is due to direct trauma or to rupture of aneurysms of the vessels within the pericardium, or to spontaneous rupture of a diseased heart wall.

Inflammation. Acute Pericarditis.—Pericarditis may be acute or chronic. The causes of acute pericarditis include infectious diseases, particularly rheumatic fever, acute tonsillitis, chorea, pyemia, extension from neighboring foci of inflammation, such as pleura, mediastinum and myocardium, and infected wounds. Terminal infections of Bright's disease, diabetes, scurvy, cancer and other chronic exhausting diseases may be manifested in the pericardium. The acute inflammations may show fibrinous, fibrinoserous, fibrinopurulent, purulent and rarely hemorrhagic exudates. Acute fibrinous peri-

carditis usually becomes fibrinoseous, and is commonly present before the other types of exudate appear. The earliest stages of the fibrinous variety may be localized to various parts of the membrane, but the process soon involves the entire surface of both visceral and parietal layers. The endothelial surface loses its gloss and a thin film of fibrin, sticky, arranged in irregular bands and of light yellow color, is seen, sometimes called the "bread and butter" pericardium, because of its fancied resemblance to the appearance of the butter after a bread and butter sandwich is pulled apart. Increase in the amount of fibrin produces the "shaggy heart" or *cor villosum*. As the fibrin is separated from the exudate, the movements of the heart whip it into thin villi and heavier bands, which occasionally are arranged spirally about the heart with the heav-



FIG. 185—Acute fibrinous pericarditis, the shaggy heart or *cor villosum*.

ier bands near the base. Visceral and parietal exudates are in contact and produce the friction rub of this disease. Histologically, there is hyperemia of the pericardium, with a moderate infiltration of leucocytes, lymphocytes and other cells of acute inflammation in the interstitial tissues, and even in superficial parts of the subepicardial fat. The endothelium has disappeared or is present as a few, swollen, degenerate cells. On the surface is a mass of fibrin in heavy bands and fine reticular mesh, enclosing leucocytes, lymphocytes and other migrating cells, and occasionally also bacteria. Organization begins very early and is often well marked within twenty-four hours of the clinical onset. This is the dry or plastic pericarditis of the clinicians. It is soon accompanied by an increasing exudate of fluid, so that the layers of the pericardium are separated and the rub disappears. The fluid is disposed as in hydropericardium, but is a cloudy, limpid fluid of relatively high specific gravity, contains cells of the exudate and tends to clot upon withdrawal. The fluid is often present in

quantities of 400 or 500 c.c. and may materially exceed those amounts. This is the so-called pericarditis with effusion. The mechanical effects of the fluid are essentially those of hydropericardium, referred to above. If the pericarditis be the result of pyemia, or other infection with pyogenic organisms, extension from neighboring suppurations or wounds, the process rapidly becomes purulent. There may be little fibrin present at any period of a purulent pericarditis, and if present early may be subsequently reduced by the lytic action of cellular and bacterial ferments. The pus may be thin and limpid or thick and viscid, depending upon the amount of exuded fluid. This is sometimes called *pyopericardium*. Histologically, the appearance of the pericardium is much the same as in fibrinous pericarditis, except for the smaller amount of fibrin and the large number of leucocytes and pus cells. Infection by gas forming organisms may lead to pneumopericardium in addition to the suppurative process. The exudate of acute pericarditis may be hemorrhagic in tuberculous



FIG. 186—Leucocytes and fibrin in acute fibrinous pericarditis.

pericarditis, in that due to hemolytic bacteria, in the irritation of the pericardium due to invasion of malignant tumors, and when pericarditis occurs in hemorrhagic diseases such as scurvy, purpura or hemophilia. Acute pericarditis is usually a part of some infectious disease, and therefore likely to be accompanied by degenerations of parenchymatous viscera and inflammatory changes in various situations. If the pericarditis be primary, which is most probable as the result of infected wounds, it may extend to surrounding structures such as pleura, lungs, mediastinum, lymph nodes and rarely to the myocardium.

Chronic Pericarditis.—Most cases of chronic pericarditis represent the cicatrization of previous acute pericarditis, and although secondary effects are progressive, the lesion itself is merely a cicatrix. Degenerative and infiltrative changes in the scar are sometimes of importance and represent retrogression. The lesion, however, is usually not literally a chronic inflammation. An unusual form of chronic pericarditis is the nodular variety, in which small, fibrous nodules 2 to 3 mm. in diameter appear on the visceral pericardium, distributed especially along the course of the coronary vessels. The nodules are epicardial and can thereby be distinguished from peri-arteritis nodosa. Extremely common are the so-called “milk-plaques” or “soldiers’ spots.” These are fairly well defined, single or multiple areas of fibrosis varying in size from a diameter of a few millimeters to several centimeters, more common on the anterior surface of the ventricles near the apex. They rarely exceed one or two millimeters in thickness and, covered by glossy endothelial surface, appear as semi-translucent or opaque plaques. They are sometimes referred to as plaques of chronic fibrous pericarditis. They may represent areas of cicatrized exudate,

and are also said to originate as the result of prolonged pressure as by a funnel shaped chest or by instruments such as the shoemaker's awl.

The most important form clinically and pathologically is *chronic adhesive pericarditis*. This is the result of organization of acute exudates. The organizing process, beginning in both visceral and parietal layers, extends through the fibrin; the two processes fuse and the resultant scar is a mass of fibrous tissue connecting the two layers. All variations are met, between the presence of one or two bands of adhesion, to complete adhesion with obliteration of the sac. This last condition is called chronic obliterative pericarditis or *synechia pericardii*. If the fibrous adhesion be limited to a small area, the movements of the

heart may stretch the connective tissue into a more or less elongated band. It is possible that adhesions may rupture and be converted into "milk plaques." If the adhesions be extensive, a hypertrophy of the heart occurs varying in degree with the extent of the adhesion and the condition of surrounding regions. The parietal pericardium is attached to the diaphragm, to the cervical fascias, to the pleura at the roots of the lungs, and by poorly defined ligamentous structures to the sternum and to the posterior chest wall. Thus, with adherent pericardium, each contraction of the heart is against the resistance of attachments to surrounding structures and necessitates in-

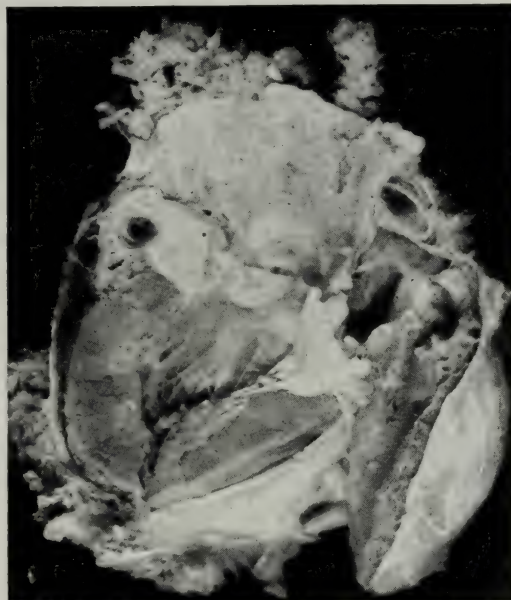


FIG. 187.—Organizing acute fibrinous pericarditis with adhesion. Note the adhesion of parietal pericardium over the flap of left ventricle.

creased muscular activity, with consequent hypertrophy. If, as is not infrequently the case, the acute pericarditis be accompanied by some inflammation of the surrounding mediastinum or a mediastinopericarditis, the organization and cicatrization of the mediastinum increases the density and extent of the external pericardial attachments, and markedly augments the resultant hypertrophy. Chronic pericarditis, either simple or adhesive, may accompany the ill-understood Pick's disease or multiple serositis, which involves pericardium, pleura and upper peritoneum.

The connective tissue of the cicatrized pericardium, whether adhesive or not, may show secondary changes such as hyaline degeneration and calcification (see Youmans and Merrill). The latter may so stiffen the pericardium as to cause resistance to muscular contraction and resultant cardiac hypertrophy.

Tuberculosis.—Rarely in adults, and slightly more often in children, the pericardium may be attacked in a generalized miliary tuberculosis. *Tubercu-*

lous pericarditis, acute or chronic, is usually the sequel of extension from lungs, pleura, mediastinal lymph nodes or bones. An acute fibrinous pericarditis may occur, but more commonly the process is chronic with increased connective tissue, often adherent, with remnants of fibrin and with fairly extensive caseation. Tubercles may be evident grossly or may require microscopic demonstration. Sometimes there is a large amount of serous exudate which may be blood tinged, or even distinctly hemorrhagic. Fibrin may be rich in amount and slightly hemorrhagic. Rarely, the exudate is purulent. Tubercle bacilli are rarely demonstrated in the exudate by staining, but the material produces tuberculosis upon injection into guinea pigs.

Syphilis.—Gummata rarely occur in the pericardium. It is possible that some forms of pericardial fibrosis may be syphilitic. Other granulomata are extremely rare.

Tumors.—Primary tumors, including fibroma, lipoma, angioma, and sarcoma are very rare. Secondary tumors are also unusual. They may be due to extension from the secondary nodules in the myocardium, or to extension from primary or secondary tumors in the mediastinum. Very rarely they may be implanted in the scanty blood vessels of the pericardium.

Parasites.—In human medicine, the echinococcus cyst is the only pericardial parasite of importance, and is rare.

ENDOCARDIUM

Congenital Abnormalities.—The mural endocardium follows related abnormalities of the heart wall. Abnormalities of the semilunar valves are not uncommon in the form of two leaflets or four leaflets. Fenestration of the leaflets in that part between the free edge and the line of closure and near the junctions is also common. These abnormalities are without functional significance. Fibrous cords stretching from one part of the surface to another, particularly in the ventricles, are of no functional importance. Small remnants of muscle may be found in the atrioventricular valves.

Degenerations.—Cloudy swelling and fatty degeneration of the endothelium may occur as a part of acute infectious diseases, poisoning by chloroform or phosphorus, and accompany inflammations of the endocardium. Calcification is common as the sequence of chronic inflammations and endocardial sclerosis. Amyloid sometimes infiltrates the subendothelial connective tissue, particularly of the right heart.

Circulatory Disturbances.—These are especially thrombosis and embolism. Emboli of infected material or bacteria may lodge in the vessels of the valves and excite valvular endocarditis. Since the valves are not vascularized to their tips, the inflammation is more likely to occur near the middle of the leaflets than upon the line of closure. This type of lesion has been studied by E. C. Rosenow, and the extent of vascularization demonstrated by Bayne-Jones. Thrombosis is really of the chambers of the heart, but has its origin in or upon the endocardium. Commonest is the inflammatory thrombosis of valve endocarditis.

Marantic thrombosis of the right auricular appendage is also common as an adherent, mottled, red and gray clot, enmeshed in the pectinate muscles, filling the appendage and sometimes extending into the atrium. This is especially common where auricular fibrillation occurs, but may be seen where death is slow and there is a long agonal period with slowed circulation. Similar thrombosis in other chambers of the heart may also occur in the latter condition. Infarction of the myocardium is followed by dilatation of the chamber in the affected part, and here mottled or laminated thrombi are observed. Degenerations of the endocardium may induce thrombosis, especially between columnæ carneæ. On the basis of any of these, thrombi, large ball-like masses, may project into the chambers. They are usually attached by a pedicle and may act as ball valves. Rarely, they break free and appear as free ball thrombi in the chamber. Degenerations and necrosis of thrombi may be the source of embolism in other organs.

Endocardial Sclerosis.—Fibrosis of the mural endocardium is common and results in more or less diffuse thickening and opacity of the membrane. It may accompany chronic valvular disease or extend from sclerosis of the valves. It is probably an essentially sclerotic lesion, but rarely goes on to atheroma or calcification. Valvular sclerosis is also common and must be differentiated from fibrosis, the sequence of acute inflammation. Valvular sclerosis is probably due to the same causes as excite arteriosclerosis, and is usually accompanied by and is a part of the latter condition. It affects the left side of the heart far more commonly than the right and is most frequent in the aortic leaflets. Although it may be localized in a part of the leaflet, especially in the auriculo-ventricular valves, it usually is diffused through the leaflets as a more or less marked fibrous thickening which reduces the translucency of the leaflets. Neighboring parts of the semilunar leaflets may become adherent for a distance of one or two millimeters, but only rarely is such adhesion extensive or of any functional significance. Hyalinization to form opaque, glossy, pale blue plaques is usually localized in small areas, as are also the soft, yellow masses of atheroma. Calcification is more frequent in the aortic valve, and tends to be disposed as nodular masses in the line of attachment of the leaflets, subsequently extending into the rings and into the adjacent parts of the leaflets. This may be sufficiently massive to produce obstruction in the orifice. The more severe forms of sclerosis may obliterate the markings of the leaflets, and lead to a thickening and curling of the free edge. Such lesions may be accompanied by retraction of the leaflets and a slight degree of insufficiency. Sclerosis of the aortic valves is usually associated with a similar lesion in the sinuses of Valsalva and aorta. Sclerosis of the mitral is usually associated with a mural sclerosis of the left atrial endocardium.

Syphilitic mesaortitis of the proximal part of the aorta may involve the aortic leaflets in what appears to be a sclerotic process. Histologically, however, the lesion seems to be of chronic inflammatory nature, and both clinical and pathological studies indicate that it is more rapidly progressive than is simple sclerosis. The process begins at the junctions of the leaflets, producing

adhesion to the neighboring sinus walls and widening of the commissures. The entire extent of the leaflets is finally involved, they show rolling of the free edges and retract. Even without dilatation of the ring, the retraction of leaflets and widening of the commissures may produce serious insufficiency (Scott).

Inflammations. Acute Endocarditis.—Clarity will best be served by discussing the anatomy of endocarditis before the etiology. Acute endocarditis may be valvular, mural or chordal. In any situation two anatomical varieties are distinguishable, acute verrucose or vegetative and acute ulcerative. Acute endocarditis is most commonly valvular, and may extend from the valves to mural endocardium and to chordæ tendineæ; only rarely is endocarditis primary in these latter situations. In fact valvular endocarditis so far predomi-

FIG. 189



FIG. 188

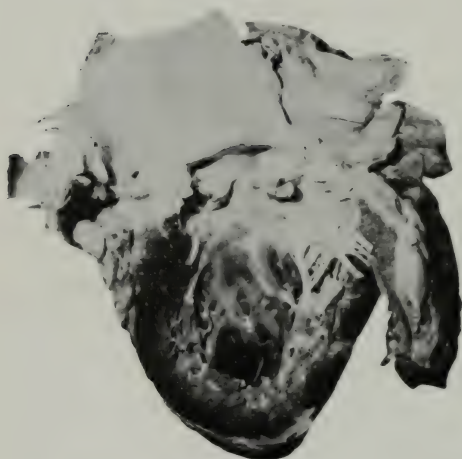


FIG. 188—Acute vegetative endocarditis of aortic leaflet. There is also a chronic endocarditis of the mitral and chronic interstitial myocarditis.

FIG. 189—Acute vegetative endocarditis upon larger leaflet of mitral valve. Dilatation of heart.

nates, that the term endocarditis as commonly employed without qualification, refers to valvulitis. Mural and chordal endocarditis are always so specified. Acute verrucose endocarditis may be of bacterial or toxic origin or both; ulcerative endocarditis is practically always bacterial.

Acute Vegetative Endocarditis usually first affects the line of closure of the leaflets, which is situated upon the ventricular surface of the semilunar and the atrial surface of the atrioventricular valves. According to Czirer, the first change is either a proliferation of endothelial cells, with proliferation of the subendothelial cells and infiltration of lymphoid and plasma cells, or edematous degeneration and necrosis of the endothelium and of the underlying tissue. These changes may be of toxic origin or due to lodging of bacteria, and are rapidly followed by the deposition of small thrombi, derived from the blood as it flows over the injured area. Grossly, in the early stages, these appear as a

row of minute, soft, friable, loosely attached, pink or pinkish-yellow nodules, one or two millimeters in diameter. In the toxic non-bacterial forms this is often the limit of change. In the bacterial forms death may occur in this stage or the lesion progress to form larger nodules. These may appear as rows of vegetations of various sizes from one to five or six millimeters in diameter, with the mass of the lesion along the line of closure, but with lateral extensions. On the other hand, there may be an apparent fusion as the thrombus increases in size so as to form a more or less hemispherical mass ten, fifteen or twenty millimeters in diameter. The larger vegetations often contain many erythrocytes and are of mottled, deep red color. They are extremely friable and often necrotic centrally or upon the surface. The lesion is essentially an inflammation of an avascular structure, in the form of a thrombovasculitis, although exudation may occur from the valves, especially after new vessels have grown near the point of irritation. This contribution is principally in the form of polymorphonuclear leucocytes. Sometimes the term acute verrucose endocarditis is applied to those cases in which the vegetations are minute, the term vegetative being applied only to those in which the masses are several millimeters or more in diameter. This usage is of some value but is not universally applied.

Microscopically the vegetation has the same general characters as a thrombus in any other situation. The earlier forms show primary deposits of platelets followed by formation of fibrin which enmeshes leucocytes and red blood corpuscles. Bacteria are often, but not constantly, present. The underlying portion of the leaflets shows disappearance of the endothelial covering, and a moderate degree of necrosis of connective tissue and elastica. There is a certain amount of fibrin formation within the tissue spaces of the leaflets, continuous with that of the thrombus, as well as a moderate infiltration of lymphocytes, leucocytes, and endothelial cells. These cells may come from the blood circulating over the leaflets or may migrate from the essential blood vessels of the leaflets. Hyperemia may be observed in the preëxisting vessels near the base of the valve. Bayne-Jones has shown that vascularization normally extends further into the leaflets than was formerly supposed. These vessels provide a point of lodgment for infectious emboli, and the latter may give rise to vegetation upon the leaflets. In this case, the lesions of the atrioventricular valves may start near the middle of the leaflets and appear upon either ventricular or non-ventricular surface, but they may be near the free edge of the semi-lunar valves. Histologically, the thrombus is the same as in those lesions starting along the line of closure, but the valve leaflets themselves under these circumstances show the phenomena of inflammation involving vascular structures.

Acute Ulcerative Endocarditis.—At any stage of the process the thrombi may undergo necrosis, more particularly when the lesion is due to direct bacterial contamination. The sloughing of the necrotic material, therefore, is likely to produce ulceration. At first this is merely an ulceration of the vegetation, but subsequently as sloughing and necrosis continue, the leaflet itself is ulcerated. The acute ulcerative endocarditis always shows in the margins either the remnants of old vegetations or new vegetations, laid down as the result

of the presence of the ulcer. When ulceration is extensive and bacteria are numerous, the condition is sometimes referred to as mycotic malignant endocarditis. Ulcerative endocarditis is usually confined to valve leaflets, but if the underlying acute vegetative process extend to chordæ tendineæ or to neighboring parts of the endocardium or to the base of the systemic aorta, the ulceration may follow and involve these structures. As a result of the ulceration, the pressure against the weakened part of the leaflet may produce a bulging away from the chamber of higher pressure, and thus produce an aneurysm of the leaflet. Perforation of the leaflet may result directly from rapidly extending ulceration or may be due to rupture of a leaflet aneurysm. In the semilunar valves such pathological perforations must be distinguished from the common fenestrations at the margins of normal leaflets.

Histologically, ulcerative endocarditis is likely to show richer bacterial content of the lesion than is true of the vegetative forms; leucocytes are more numerous and the condition may be distinctly suppurative in character.



FIG. 190—Acute vegetative endocarditis of aortic valve with beginning ulceration.

In the morbid anatomical diagnosis of endocarditis, it is important to remember that normally the free edges of the atrioventricular leaflets are somewhat thick and nodular, and that in the semilunar valves the corpora Aurantii may be of considerable size. In infancy and early childhood the atrioventricular

valves may also be the seat of fairly soft fleshy masses (noduli Albini), remaining after the condensation of connective tissue in the rest of the valve. Not infrequently the atrioventricular leaflets of infants show small, dark red, nodular masses. The exact nature of these is subject to differences of opinion; some regard them as small hematomas; others as dilated persistent blood vessels and still others (Nichols) as true angiomas.

Sequels of Acute Endocarditis.—The breaking down of the valvular vegetation may be an important source of embolism. If the emboli contain few or no bacteria the resulting infarct may be bland. A fairly rich content of bacteria may result in septic infarction and multiple abscess formation. It sometimes happens that the primary source of infection from which the endocarditis arose disappears, but the bacteria may persist and multiply in the valve lesions and be a continual source of discharge of bacteria into the circulating blood. As with other acute inflammations, organization and cicatrization occur to produce the so-called chronic endocarditis. The minor degrees of acute endocarditis lead to no functional disturbance of the valve orifice, but larger vegetations may

lead to failure of apposition of the lines of closure and resulting regurgitation of blood, or more commonly may result in obstruction of the orifice. Lesions primary upon the valve may extend to the mural endocardium and to the aorta, but only rarely to the pulmonary arteries. The more serious ulcerative and suppurative lesions may extend into the myocardium and indeed through the myocardium to the pericardium. Inasmuch as acute endocarditis is part of an



FIG. 191—Acute ulcerative endocarditis of aortic valve, with extension to the ventricular endocardium.

infectious process, secondary degenerations in parenchymatous viscera, acute splenic hyperplasia, anemia, nephritis, etc. are likely to be observed. Recovery of the patient is accompanied by local organization, cicatrization and the production of a chronic endocarditis. This will be discussed after considering the causes of acute endocarditis.

Subacute Endocarditis.—Various classifications of endocarditis, usually representing the personal views of authors, have been offered but cannot as yet be accepted. It is said that acute rheumatic endocarditis is found solely as the verrucose form along lines of closure, and acute bacterial endocarditis

produces the more massive vegetative lesions, but this view cannot be regarded as finally established. Subacute bacterial endocarditis, or endocarditis lenta of Schottmüller, is a disease of several months duration. Anatomically the lesions affect especially the mitral or aortic valve or both, are coarsely vegetative, often involve chordæ tendineæ and mural endocardium and show variable degrees of slowly progressing organization and cicatrization. Libman has correlated the clinical and pathological features of a large group of such cases and finds that there are bacterial, or septicemic, and abacterial stages. Although there is some disagreement among investigators, Wright states that bacteria seem to be alive in the vegetations in the abacterial or non-septicemic stage. Libman and others find a high incidence of streptococcus viridans with a few cases due to bacillus influenzae or other organisms. Nevertheless, other



FIG. 192—Acute ulcerative endocarditis of mitral valve, with extension to mural endocardium of ventricle and atrium.

workers get different results and Lämpe reports a considerable proportion due to streptococcus hemolyticus. Clawson, in an excellent study, reaches the conclusion that factors of virulence and resistance rather than the kind of organism determine the course of endocarditis.

Causes of Endocarditis.—Acute endocarditis is practically always secondary to infection elsewhere. Occasionally there appears to be no other primary focus, either because it is hidden and undiscovered or perhaps because bacteria have gained access to the blood stream without producing a lesion at the point of entrance.

The commonest cause of acute endocarditis is rheumatic fever. According to Aschoff, the latter disease is complicated by acute endocarditis in from 10 to 20 per cent. of cases, and about 60 per cent. of all inflammatory valvular disease is of rheumatic origin. Acute rheumatic valvulitis may be accompanied by the presence of bacteria in the blood stream and in the lesion, particularly

streptococci, principally streptococcus viridans. Other bacteria are sometimes encountered and many cases show no bacteria. Owing to the doubtful etiological relation to rheumatism of the diplococcus of Poynton and Payne, and the inconstancy of bacteriological findings in rheumatic endocarditis, it seems likely that the organisms recovered are secondary invaders.

Pneumonia, osteomyelitis, septicemias and pyemias resulting from wounds or the infections of childbirth, typhoid fever, measles, scarlatina, diphtheria, tuberculosis, gonorrhea and other infectious diseases may be complicated by acute endocarditis. Septicemias and pyemias, especially those due to streptococcus hemolyticus and staphylococcus aureus, are particularly likely to produce ulcerative endocarditis. Much consideration has been given to chorea as

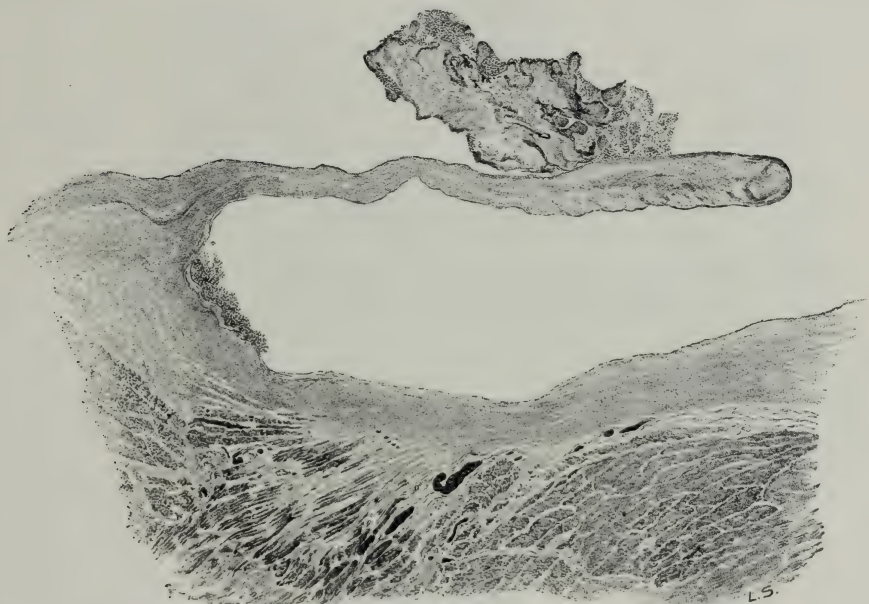


FIG. 193—Low power drawing of acute vegetative endocarditis of aortic leaflet.

a cause of endocarditis. Prior found a coincidence of the two in 5 of 92 cases of chorea, which probably represents a maximum. Acute endocarditis complicated pneumonia in 4 per cent. of Wells' 517 cases and in 3.6 per cent. of Locke's 835 cases. The pneumococcus was recovered in less than half of Locke's cases of endocarditis, and type 1 was found to be the most frequent invader. Rosenow believes that many of the non-hemolytic streptococci of endocarditis are altered pneumococci, but this view is not generally accepted. Similarly, other infections such as typhoid fever and diphtheria may be complicated by endocarditis, but the lesion is more commonly due to secondary invasion by streptococci, staphylococci, pneumococci, etc., than by bacillus typhosus or bacillus diphtheriæ. The same is true of influenza; endocarditis due to the bacillus influenzae, however, does occur more particularly in connection with subacute endocarditis as reported by Libman and Celler, Cohen and Greenberg and others. The uncommon endocarditis of epidemic meningi-

tis is usually due to the meningococcus. True gonococcal endocarditis is not so rare as many suppose. Thayer finds that although the left side of the heart is most commonly affected, the right side is more often attacked than in rheumatic endocarditis. The term simple toxic endocarditis refers to an inflammation of the endocardium as the result of toxic substances in the blood. This condition is observed in late tuberculosis and in other chronic diseases. Cultures fail to show bacteria and it is therefore supposed that the condition is toxic. This assumption cannot be finally accepted for cultural methods are not yet perfect, and it is possible that bacteria may produce the lesion and subsequently disappear. In a few cases, tubercle bacilli have been found in the vege-

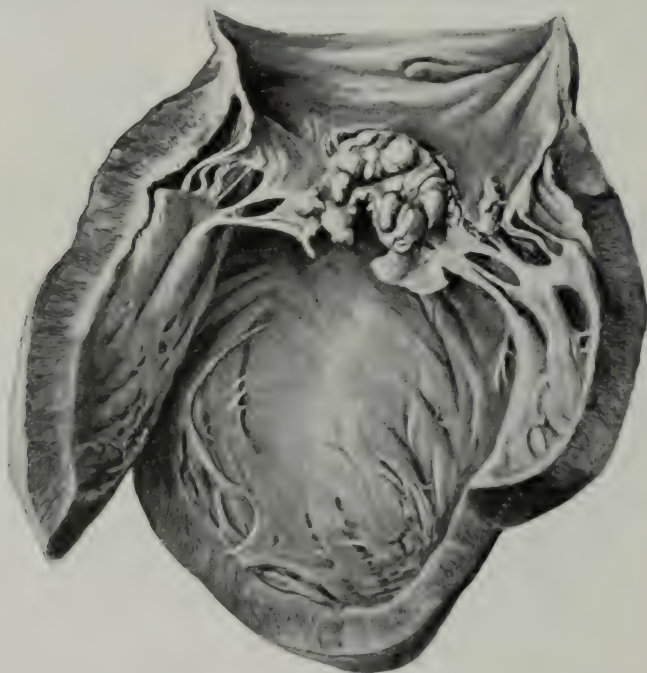


FIG. 194—Acute ulcerative endocarditis of mitral valve, with extensive destruction of leaflet.

tations, but it is easily possible that they may be implanted after the lesion develops, owing to the fairly common terminal appearance of tubercle bacilli in the blood stream.

Although there are numerous exceptions, Thayer states that in a general way the severity of acute endocarditis may be classified in ascending order of severity as due to bacillus influenzae, streptococcus viridans, gonococcus, staphylococcus albus, staphylococcus aureus, pneumococcus, streptococcus hemolyticus.

Experimental acute endocarditis was produced in rabbits by Ribbert, who injected potato particles to injure the valves and staphylococci to produce the lesion. Wyssokowitsch used powdered charcoal instead of potato. Fulci was unable to produce an endocarditis by the use of charcoal and toxic

extracts of bacteria. Numerous authors including Lissauer, Fulci, Horder, Fox and others have produced endocarditis by the injection of organisms without trauma to valves. Rosenow has studied the matter extensively and has been able to produce endocarditis in rabbits without trauma to valves. His best results were obtained with organisms freshly isolated from human cases, and grown so that they clump in cultures and adhere to test tubes. He believes that embolism in valvular vessels produces the lesion, which is true in his experiments. The rabbit lesions, however, were not usually distributed along the line of closure as is so common in man, and it is doubtful that his results are uniformly applicable to man.

For many years there has been much study of the point of origin of valvular endocarditis. Most early cases in man show the lesions at the line of closure, and it has been assumed that the trauma at this point renders the endocardium susceptible to the action of toxic agents, or by actual injury to the endothelium provides a point of lodgment for bacteria. On the other hand, occasional cases are seen in which the lesion apparently starts in the middle or near the base of the leaflet. These may well be due to infected emboli in valve vessels. In our opinion, experimental investigation has not solved the problem. Certainly it seems that in the hands of most investigators, trauma to leaflets gives a greater ratio of success. It must also be accepted that most of Rosenow's rabbits showed embolic lesions. Our opinion is that, although not infrequently embolic valvular endocarditis is observed in man, most cases originate in the line of closure due to deposition of bacteria at a point of injury or lowered resistance, due to the mechanical factors of valve function.

Chronic Endocarditis.—Organization and cicatrization of acute endocarditis produces a mass of scar tissue more or less coextensive with the original lesion. It is possible that progressive fibroplastic growth takes place, but more reasonable to suppose that subsequent changes are due to secondary changes in the scar. The endocardium shows masses of scar tissue, more or less nodular, replacing the thrombi. Inflammatory changes in the substance of valves or mural endocardium lead to fibrosis. The scar tissue often shows hyalinization,

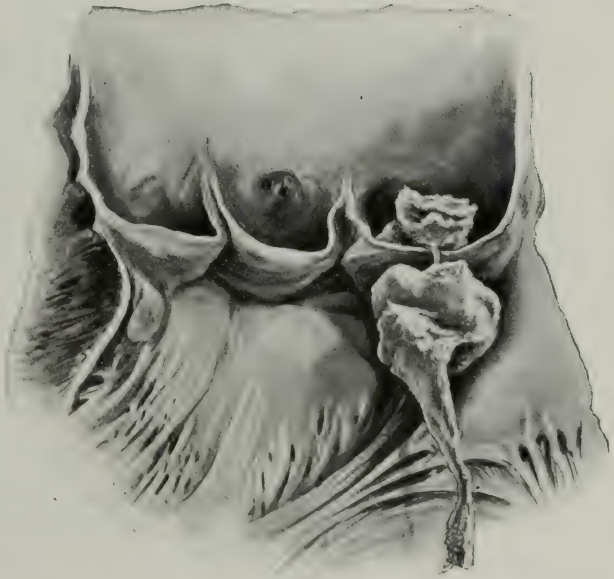


FIG. 195—Acute ulcerative endocarditis of aortic valve, with extension through leaflet and vegetation upon aortic surface.

sometimes necrosis and even calcification. Most important are thickening, stiffening and fibrous adhesion of leaflets, and retraction of leaflets and chordæ tendineæ. Density and retraction may progressively increase and cause progressive symptoms. The adhesion and thickening produce obstruction in the valve orifice; the retraction permits regurgitation. The leaflet in chronic endocarditis shows fibrous, often somewhat nodular, thickening most marked near the edge; the remainder of the leaflet is moderately or markedly thickened but may show little change. Sometimes the free edge may be thin and pliable, but is usually involved in the fibrosis of the line of closure. The semilunar leaflets may show curling of the thick edge. Not infrequently blood vessels,



FIG. 196—View from above of chronic aortic valvulitis with stenosis.

persisting after their growth to partake in organization, are seen upon the surface of the leaflet. Adhesion and retraction are common, especially in the atrio-ventricular valves; the chordæ tendineæ may show the same changes. Calcification is more common at the base of valves or in areas of adhesion than along the free edge. Histologically, the endothelium is present over the surface, the fibrous connective tissue dense and often hyalinized, blood vessels scant. Necrosis is not common, but there may be small or larger areas of calcification.

Certain features vary slightly in different valves, necessitating brief consideration of lesions and effects in each area. In the

following discussion, reference is made particularly to chronic valvular disease. Similar abnormalities of valve function may be due to acute endocarditis, but in this case secondary hypertrophies are not likely to be observed because, (a) the acute lesion is not of sufficient duration to produce hypertrophy, and (b) because the muscle is usually the seat of degeneration and in no condition to undergo hypertrophy.

Mitral Stenosis.—In mitral stenosis, the orifice may be only slightly narrowed or so contracted as barely to admit a pencil. The stenosis is due to adhesion between the leaflets and is sometimes augmented by projecting calcareous masses. The leaflets therefore show adhesion, thickening particularly near the free edge, thickening and often adhesion of chordæ tendineæ with fibrosis of the apices of papillary muscles.

Acute vegetations are often present as the result of a terminal infection of

the same, or other nature, as that causing the original lesion, or due to erosion of calcified areas. Retraction of leaflets may produce insufficiency or, if adhesion be extensive, may emphasize the stenosis. Retraction of chordæ tendineæ may or may not produce insufficiency, depending upon the degree of adhesion and stiffening of the leaflets. More severe degrees of stenosis appear as the "funnel shaped" valve due to retraction of the chordæ, or as the "button hole" valve when the leaflets are so stiff as to form a diaphragm with only a slit-like orifice.

Mechanical models show that in mitral stenosis, systemic and pulse pressure fall and venous pressure rises. In life it is probable that in milder degrees of stenosis the slow diastolic filling of the left ventricle is compensated by in-

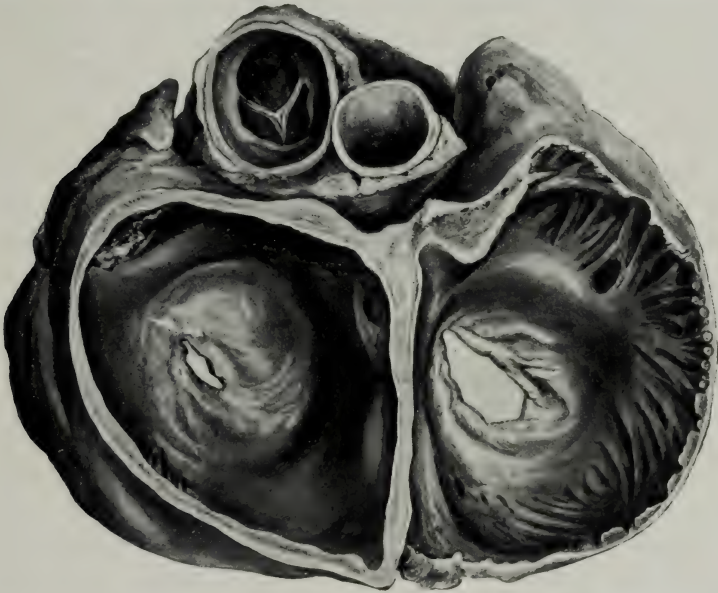


FIG. 197—View from above of chronic valvular endocarditis with stenosis of aortic, mitral (button hole) and tricuspid orifices.

creased contractile force of the left atrium. The importance of atrial systole in normal cardiac function has been emphasized by Feil and Katz. More severe degrees are not compensated; pulmonary stasis and increased pressure in the pulmonary artery throw increased work upon the right ventricle. Only when the right ventricle fails and the tricuspid ring dilates, is there systemic venous hyperemia. These physiological alterations lead to hypertrophy of the left atrium, hypertrophy of the pulmonary artery often associated with arteriosclerosis, and hypertrophy of the right ventricle. The continuity of the spirally arranged musculature of the heart probably accounts for the slight hypertrophy of the left ventricle, which is sometimes observed. Atrial fibrillation is common in mitral stenosis, and probably increases the incidence of thrombi in the atrial appendage. Chronic passive hyperemia of the lungs or brown induration is almost constant, but general systemic hyperemia is variable in degree.

Mitral stenosis is common, is usually due to acute rheumatic endocarditis,

and is a disease of early and middle life, being unusual after the fifth decade. It affects women more often than men. Physical examination may disclose the enlargement of the left atrium and right ventricle, sometimes confirmed by roentgenologic studies. Murmurs appear late in diastole or merging with the first sound of the heart (presystolic). The left auricular hypertrophy may give a large, sometimes notched, P wave in the electrocardiogram. The right ventricular hypertrophy may invert the R wave in all leads, that of the second lead being smaller than that of the third. The pulse may be normal or may become arrhythmic when atrial fibrillation occurs. Blood pressure is usually normal but pulse pressure may be reduced.

Mitral insufficiency occurs with or without mitral stenosis. In either case, it is due to retraction of the leaflets, chordæ tendineæ or both. Minor degrees of mitral insufficiency are common. The leaflets show slight thickening and retraction, usually of inflammatory origin, but sometimes due to sclerosis of the valve or to organization of hemorrhages within the valves. Mechanically, the atrial pressure rises and the mean arterial pressure falls. The increase in atrial pressure is probably due rather to transfer of hydrodynamic pressure from the ventricle than to any large regurgitation of blood. Consequently, unless the myocardium fails, there is not likely to be serious pulmonary hyperemia or elevation of pulmonary arterial pressure. The tension in the atrium may induce increased effort and slight hypertrophy, but the latter is rarely marked. The high atrial pressure increases the initial tension in the ventricle and may thus lead to increased output and slight hypertrophy. Moderate degrees of mitral insufficiency produce little alteration of circulation and only slight or no hypertrophy of left atrium and ventricle. Dilatation of these chambers may finally occur with stasis, primarily in the pulmonary and ultimately in the general circulation.

Relative insufficiency of the mitral orifice may result from failure of the myocardium, with consequent stretching of the ring and sometimes of the papillary muscles. The first prevents apposition of leaflets and the second allows them to override into the atrium with leakage.

Clinically there may be no symptoms, and often the systolic murmur is discovered only during some routine physical examination. Enlargement of the left atrium may be demonstrated by physical examination and the roentgenogram.

Aortic Stenosis.—Pure aortic stenosis is the most uncommon of lesions in the left side of the heart. It occurs much more often in men than in women. The age at which it occurs depends upon the nature of the lesion. The obstruction to the orifice may be the result of a serious acute endocarditis, with thickening and adhesion of the leaflets such as occurs in mitral stenosis. Under these circumstances, however, it is common to find that the leaflets are curled along the edge, or retracted, so as also to cause insufficiency. A simple sclerotic thickening of the valve leaflets often has no functional significance, but at times the valve may become so stiffened as to prevent free opening or complete closure. This may be emphasized by the presence of large, calcareous masses in

the sclerotic process. Syphilitic disease of the root of the aorta may involve the valve so as to cause extreme stiffening. In valvular syphilis, however, retraction of the leaflets is usually more prominent. In a circulation apparatus, the production of aortic stenosis leads to an elevation of intraventricular pressure, and a fall in mean blood pressure and in pulse pressure. Animal experiments show the same conditions. It is found, however, that the intraventricular pressure rises more sharply than normal and the ejection of blood is under increased pressure. The period of ejection is prolonged and the normal amount of blood is discharged into the arterial system, except when the stenosis is very marked. As a rule, the total period of systole and diastole remains normal in time. Only when the stenosis is very great or the myocardium extremely weak does the pulmonic pressure increase, and this is maintained in spite of a fall in venous pressure. It is obvious then, that the important effect upon the heart is increased work of the left ventricle. This leads to hypertrophy of the myo-



FIG. 198—Chronic aortic valvulitis, with retraction of leaflets and curling of their edges (insufficiency) and a superimposed acute vegetative valvulitis.

cardium of that chamber, and because of the continuity of the musculature of the heart, may be found in that of other chambers. The left ventricular hypertrophy of aortic stenosis is practically never so marked as is that of aortic insufficiency. Clinically, the systolic murmur transmitted into the neck is often accompanied by a thrill. The radial pulse is likely to be small and rises slowly. Physical examination shows enlargement of the left ventricle, usually confirmed by the roentgenogram. The electrocardiogram shows inversion of the R wave in lead III. Cardiac arrhythmias sometimes accompany the disease and are usually in the form of premature systole or pulsus alternans.

Aortic Insufficiency.—This lesion is much more common than stenosis. Dilatation of the ring may occur secondary to dilatation of the heart. The pathological features of aortic insufficiency are variable. Leaflets may be so stiffened by sclerosis as to prevent their closure. A similar effect is caused by the scarring or cicatrization of valve leaflets subsequent to acute endocarditis. In both these instances, the thickening and retraction usually cause, in addition to the insufficiency, variable degrees of stenosis. Uncomplicated aortic in-

sufficiency is most commonly due to syphilis of the base of the aorta involving the aortic ring. Pearce found that 41 per cent. of clinical cases of aortic insufficiency gave a positive Wassermann test, as contrasted with 23 per cent. of other valve lesions. Pathologically, the incidence of syphilis is probably higher. In these instances, a characteristic syphilitic mesaortitis affects the root of the aorta with little or no effect upon the valve leaflets. The dilatation of the ring does not permit of complete apposition of the leaflets, although in our experience cases occur in which the leaflets have become somewhat enlarged to meet

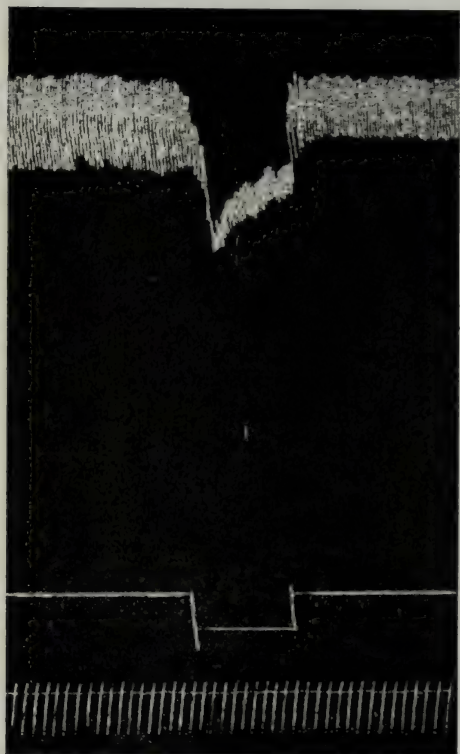


FIG. 199—Tracing of aortic stenosis in the dog, produced by means of a slip ligature about base of aorta. Signal line is also base line. Time in two seconds. Note fall in mean and pulse pressures.

the needs. Not uncommonly, however, the syphilitic disease extends into one or more of the leaflets, producing some thickening, retraction, and in some cases almost complete destruction of the leaflets, thus adding to the difficulty of closure. The lateral margins of the leaflets are often adherent to the ring, and thus apposition is prevented at the leaflet junctions as well as elsewhere. Insufficiency may be due to rupture of diseased leaflets as the result of extreme muscular effort or trauma, but may rarely occur in a normal valve (Howard). In the mechanical circulation apparatus there is a marked fall in diastolic pressure. The systolic pressure may remain normal or fall slightly. The diastolic pressure in the ventricle is likely to rise sharply just before systole. In animals much the same effect is observed, but in our own experience we have usually found a distinct fall in systolic pressure. At any rate, the mean arterial pressure is reduced. There has been much discussion concerning the fall in diastolic pressure. The rise in intraventricular pressure is due to an increased initial pressure and the ejection of a larger quantity of blood. Wiggers has examined the question of fall in pressure and comes to the conclusion that this is not due to peripheral dilatation of the vessels, but rather to a back leak of pressure with or without appreciable back flow of blood. Bazett, however, believes that there must be a back flow of blood. The pressure in the left atrium and in the pulmonary circuit remains unchanged until the cardiac muscle fails. Stewart and Hirschfelder found that during diastole the tonicity of cardiac muscle is increased. The back leak of pressure, the increased tonicity of cardiac muscle, and perhaps also

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the ejection of larger quantities of blood, result in hypertrophy, principally of the left ventricle. The hypertrophy of aortic insufficiency produces extremely large hearts, only exceeded in our experience by those due to chronic elevation of blood pressure and chronic adhesive pericarditis. Clinically, the murmur occurs early in diastole, replacing the cardiac second sound, and is sometimes musical in character. Pallor, capillary pulsations and mental symptoms are observed. The great hypertrophy of the left ventricle is accompanied by a certain amount of hypertrophy of other chambers. Percussion and the orthodiagram reveal an elongation of the heart. The systolic blood pressure is normal or sometimes increased, whereas the diastolic pressure is considerably reduced, often to figures of 60 to 30 mm. of mercury. Although it is not neces-

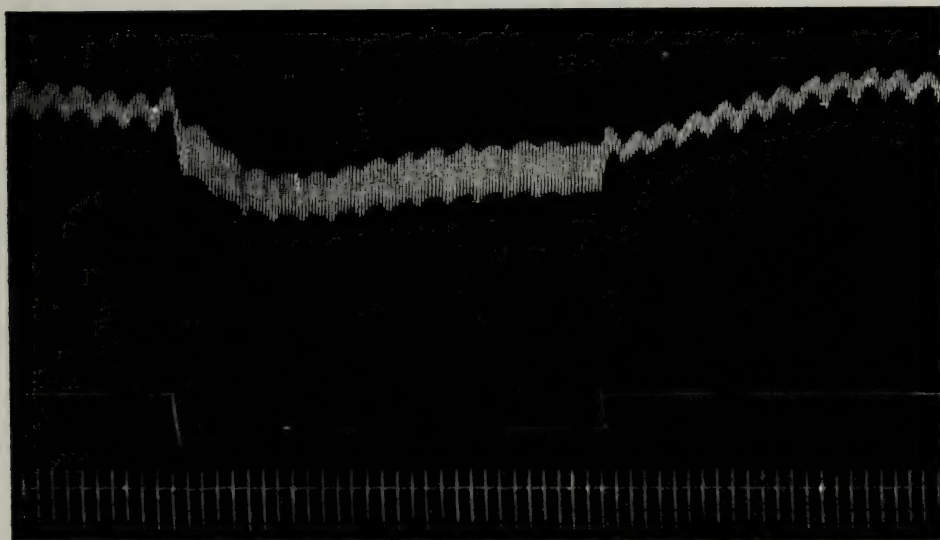


FIG. 200—Tracing of aortic insufficiency in the dog, produced with the Wiggers cannula. The signal line is also the base line. Time in two seconds. Note the fall in mean pressure and the increase in pulse pressure. Vasoconstriction tends to increase mean pressure and, after termination of insufficiency, elevates general pressure level.

sary physiologically to explain the high systolic pressure as due to organic disease, nevertheless, in our own experience this is usually associated with some disease influencing peripheral circulation. According to Wiggers, the Corrigan, "water hammer," or collapsing pulse is due not so much to back flow of blood out of the vessel, as to the sharp impact of the increased and sudden discharge into the vessel.

Valves of Right Side of Heart.—The most common affection of these is a relative tricuspid insufficiency, which usually occurs as the result of dilatation of the right ventricle and atrium. This diminishes the muscular support of the ring and chordæ tendineæ, so that the leaflets do not appose. This accounts in large part for the venous stasis of decompensated hearts. Acute tricuspid valvulitis occurs in connection with acute endocarditis of the left heart but is unusual. We have observed minute vegetations in septicemias. The importance of gonorrhea in right sided lesions should not be overlooked (Thayer). Chronic

lesions are nearly always associated with chronic lesion of the left side (Herrick). In our experience, chronic tricuspid valvulitis produces stenosis much more often than insufficiency, but they are likely to be combined.

Pulmonary insufficiency is uncommon but occurs as the result of dilatation of the ring in decompensation, acute or chronic endocarditis, sclerosis of leaflets, aneurysms or rupture of cusps, congenital anomalies, but only rarely if ever, as a result of arteriosclerosis of the pulmonic aorta. The principle causes of pulmonic stenosis are lesions due to endocarditis, acute or chronic, and congenital stenosis of the conus, ring, or root of the pulmonic aorta. We have observed two cases of pulmonic stenosis, as the result of bulging of sacular aneurysms of the root of the systemic aorta and of the aortic sinus of Valsalva. The principles of circulatory disturbance must be much the same as those in the left side of the heart; such studies as have been made confirm this view (MacCallum, MacCallum and McClure).

Tumors of Endocardium.—In addition to the tumor-like embryonal remnants of blood vessels in valves, myxomata and fibromyxomata may occur. Muscle remnants in valves are not to be confused with tumors. Certainly, however, confusing pictures may be presented by sharply focalized sclerosis and by organizing blood clots. Rarely, a malignant tumor may metastasize into the endocardium, but as a rule such metastases are really in the myocardium and project into the endocardium.

MYOCARDIUM

Introduction.—In presenting this phase of the subject of heart disease, time and space will be conserved by including certain abnormal conditions of the heart as a whole, because many of the diseases of the myocardium are intimately related to the entire organ.

Congenital Anomalies.—The heart develops from a primary tube which becomes tortuous to form the S shaped tube, and develops septa and valves to form the four chambered organ. At any time in this period of development, interruptions, alterations and inflammatory lesions may occur to produce an anomalous heart. These may be so slight as to be of no functional importance, or on the other hand may seriously cripple the heart or be incompatible with life. The heart may be absent (acardia), or rudimentary (hemicardia); it may project through the anterior body fissure (ectopia cordis). It may be transposed in position so that the greater ventricle is to the right and the apex points to the right (dextrocardia). This may be associated with complete transposition of the viscera, or with transposition of the great vascular trunks. In addition to other clinical evidence, the electrocardiogram shows inversion of the curves of lead I and an interchange of the curves of leads II and III. A pathological, rather than anomalous dextrocardia may be caused by lesions of the chest such as pleural effusions, adhesions, tumors, etc., but the chambers are not transposed. The electrocardiogram may be abnormal but not in the same way as in anomalous dextrocardia. The commonest anomaly of the heart is a patent foramen ovale. This may be merely a slight defect demonstrable only

by a probe and establishing no real communication between the atria, or the opening may be widely patent and easily visible. There may also be deficiencies of the interatrial septum and of the interventricular septum. Thus, trilocular or even bilocular hearts may be formed. Congenital atresias of orifices may be due to faults of development or to fetal inflammations. The coronary arteries are not infrequently anomalous.

Depending upon the direction of the blood in patencies of the ductus arteriosus or the septa, these openings may give rise to venous arterial shunts or arterial venous shunts (Abbott and Dawson). Although there is divergence of views, Holman holds that the cyanosis of cardiac anomalies is due to inflow

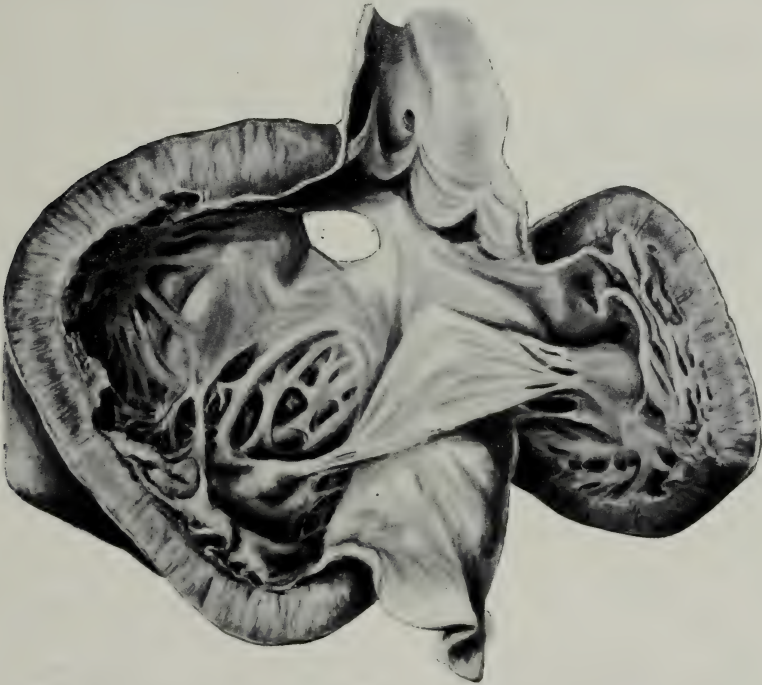


FIG. 201.—Congenital perforation of interventricular septum of heart in the usual situation at the cephalad portion.

of venous blood into the systemic circulation. This cyanosis (*morbus ceruleus*) may be marked, slight or absent, depending upon the amount of unaërated blood. The right heart is the seat of hypertrophy variable in degree. Holman attributes the hypertrophy to two factors, (a) added effort necessary for propulsion of an increased minute volume flow of blood and, (b) the fact that the abnormal opening forces the right side to propel part of its blood against the systemic, peripheral resistance. For further discussion the reader is referred to M. Abbott, Keith, Mönckeberg, Schlegel, Hirst and Piersol, and Schwalbe.

Degenerations. Cloudy Swelling.—Cloudy swelling of the myocardium occurs in many acute infectious diseases such as diphtheria, scarlet fever and others, may be the result of poisons such as phosphorus, arsenic, chloroform, iodoform, ether, alcohol, and may be due to anemia, either acute or chronic,

primary or secondary. It is of importance to note that these agents cause general cloudy swelling, and that the affection of the heart is only a part of a more widespread, similar lesion. Grossly, the heart may be dilated and the muscle is likely to be soft, flabby and cloudy. The cut surface bulges, shows a cloudy brown or boiled appearance and is more friable than normal. Microscopically, the muscle fiber cells are swollen, show diminution or loss of transverse striation, and may contain acidophilic granules. Slight nuclear changes such as pyknosis may be noted without indicating true necrosis. A pathological diagnosis must take into account the length of time the individual has been dead, because postmortem changes may very closely simulate those of cloudy swelling. There are no constant changes clinically, but often low blood pressure, cardiac dilatation, rapid rate and sometimes arrhythmia may be associated. The nature and cause of the arrhythmia are not clearly understood. Bradycardia may occur and is presumed to be due to similar lesions in the conduction system.

Fatty Degeneration.—This is due to essentially the same causes as those of cloudy swelling, operating over a longer time or with greater intensity. Grossly, the heart is soft and flabby and has a dull, opaque appearance. If the fatty degeneration be diffusely scattered throughout the heart, the muscle has a dull yellow color; if, as is more commonly the case, the fat be irregularly distributed in the muscle, the so-called “tigroid” or “tabby cat” appearance is produced. This tigering is often seen better through the endocardium of the right ventricle than that of the left, and is likely to be more prominent in the papillary muscles than in the columnæ carneæ. It is seen best through the endocardium as short, parallel lines of yellow color, about a millimeter in width and separated about a similar distance from adjacent lines. Microscopically, the change is satisfactorily demonstrated only by the use of special stains such as osmic acid, Sudan III or Scharlach R. For this purpose, formalin fixation must be employed. Master emphasizes the fact that a gross diagnosis of fatty degeneration often fails of confirmation microscopically. He finds that a certain amount of fat is normally present, particularly in the sarcoplasm between the muscle fibers and arranged in longitudinal and transverse rows. The diagnosis depends then not merely upon finding fat droplets in the muscle, but rather upon finding them in considerable numbers, and associated with other degenerative changes such as disappearance of transverse striations and nuclear degeneration. As with cloudy swelling, there is no constant clinical picture. Low blood pressure, rapid or slow heart, and sometimes cardiac arrhythmia are observed.

Fat Infiltration.—This is fairly common, especially in obese patients. The entire heart is usually enlarged but not necessarily so, and may be atrophic. There is an increased amount of subepicardial fat, which upon transverse section of the myocardium is seen to extend in irregular lines between the muscle fiber bands. Microscopically, this is observed in the form of fat cells between muscle fibers and groups of muscle fibers. Not uncommonly, there is a certain degree of atrophy of the muscle substance. In the more severe cases, this produces a certain amount of weakness of the heart muscle which is par-

ticularly evident upon exertion. Ordinary degrees of fat infiltration appear to be without any influence upon cardiac activity.

Other Degenerations.—Amyloid, as has been noted, occurs under the endocardium, particularly on the right side of the heart. It may also be found in the smaller divisions of the coronary arteries. Simple hyaline degeneration does not affect the muscle itself, but is sometimes observed in the connective tissue when it is increased between the muscle fibers. Zenker's hyalin is discussed under the heading of necrosis. Calcification of the myocardium is observed most particularly in areas of necrosis or in areas of extensive fibrosis. It is seen also in the so-called calcium metastasis, more especially in the right heart.

Segmentation of Myocardium.—Practically never in infancy, rarely before the twentieth year and increasing in frequency as age advances, the myocardium may show histologically, numerous transverse fractures of the muscle fibers. Lateral enlargement between fractures is slight or absent and neighboring reactive inflammation never observed. It is usually stated that segmentation occurs in the line of the intercalated discs, and that a slightly different condition called fragmentation shows fractures of the fibers between, and not necessarily involving the discs. The studies of Saphir and Karsner, as well as of others, show that in both, the fractures are in the intercalated discs, the differences in appearance being due to differences in number and conformation of the discs under various circumstances. Aschoff attributes the change to postmortem decomposition, but we found that it can be produced in rabbits by suddenly elevating intraventricular pressure and producing dilatation, and that animals can live for at least forty-eight hours with the lesion. Grossly, the heart of segmentation may be soft, flabby, and dilated, but shows nothing characteristic of segmentation.

Necrosis.—This is most likely to appear as a sequence of degeneration, as a part of acute myocarditis of infectious diseases, or as the result of occlusion of branches of the coronary arteries. In the last instance, it is massive coagulation necrosis, to be considered under circulatory disturbances. In the others, it appears as focal areas either of hyaline or granular necrosis, or as Zenker's hyaline necrosis with lateral swelling and rupture of fibers. Usually more or less marked inflammatory reaction is found in the neighboring interstitial substance.

Circulatory Disturbances.—General anemias may be acute or chronic. In the former, such as occurs following large hemorrhage, the heart is pale,

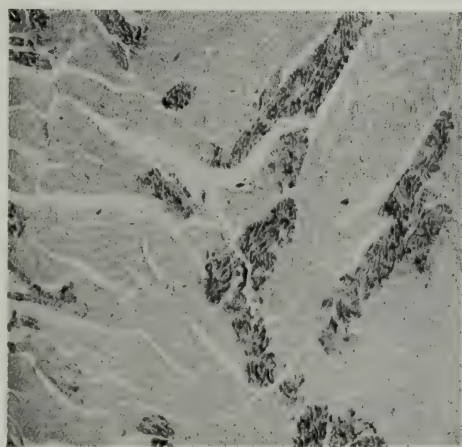


FIG. 202.—Foci of hyaline of necrosis myocardium of dog, due to experimental coronary occlusion.

grayish-red or grayish-yellow, but differs from the heart of fatty degeneration in that it remains firm. Prolonged anemias from repeated smaller hemorrhages or as the result of exhausting diseases or chronic blood diseases, lead to more or less widespread fatty degeneration.

Local anemia of the myocardium is due to disease or occlusion of branches of the coronary arteries. The term anemia in this connection refers to reduced access of blood rather than absence of blood. If occlusion be sudden, the affected area is likely to be slightly hyperemic rather than anemic before proceeding to necrosis; if gradual, atrophy of muscle and fibrosis ensue. The pathological

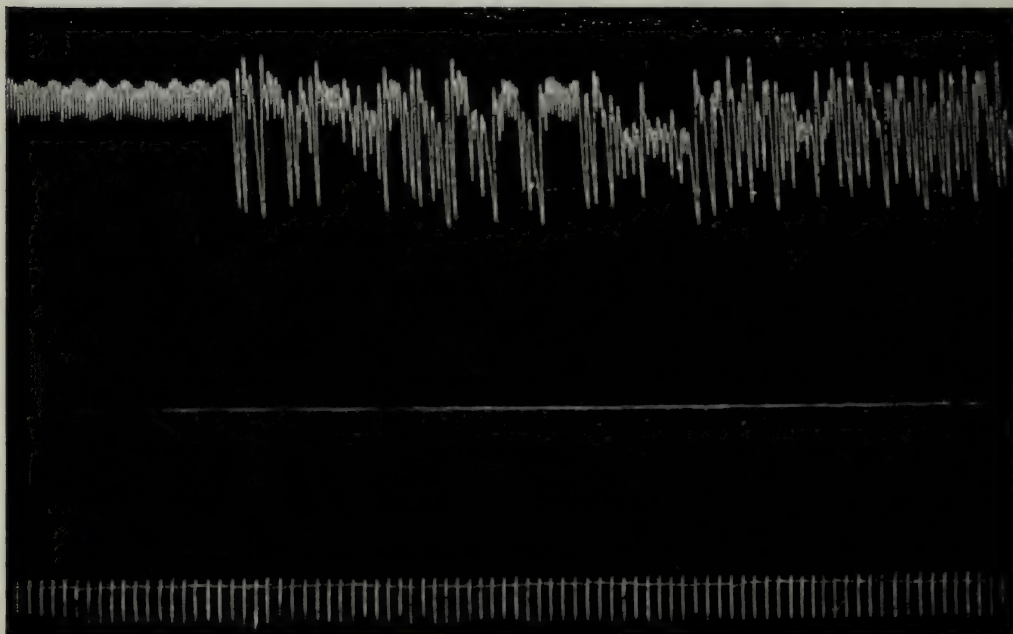


FIG. 203.—Tracing of cardiac arrhythmia in the dog, incident to experimental acute myocardial necrosis produced by multiple injections of 95 per cent. alcohol into the myocardium. The injections were made before this tracing was made, so that the arrhythmia follows a period of normal mechanism. Time in two seconds.

anatomy of coronary closure concerns itself with these two conditions, namely, infarction and focalized atrophy and fibrosis.

Infarction.—The branches of the coronaries enter the myocardium and spread out toward the endocardium. Whereas anastomosis of the larger vessels may be considerable, as pointed out by Gross, the smaller vessels communicate only in a limited way through capillaries. The area of occlusion therefore, rapidly undergoes necrosis. The infarct is generally conical in shape with the apex near the epicardium and the base toward the endocardium. Karsner and Dwyer found experimentally that there is first hyperemia, then coagulation necrosis. The area gradually undergoes decolorization, becomes smaller, more sharply defined, removed from the site of arterial occlusion and in the late stages is accompanied by thinning of the heart wall. There is only rarely a zone of reactionary hyperemia; fibrosis appears first in the margins and finally ex-

tends throughout the infarct. In man the lesion is usually seen either as a recent white infarct or as an area of cicatrization. In the early stages the infarct is a swollen, soft, fragile, sharply defined, pale yellow, variously truncated conical area, with the base toward the endocardium. In later stages, this is reduced in size and the cicatrization proceeding from the margins may leave a streak of unorganized, yellow necrotic material near the center. The scar retracts and

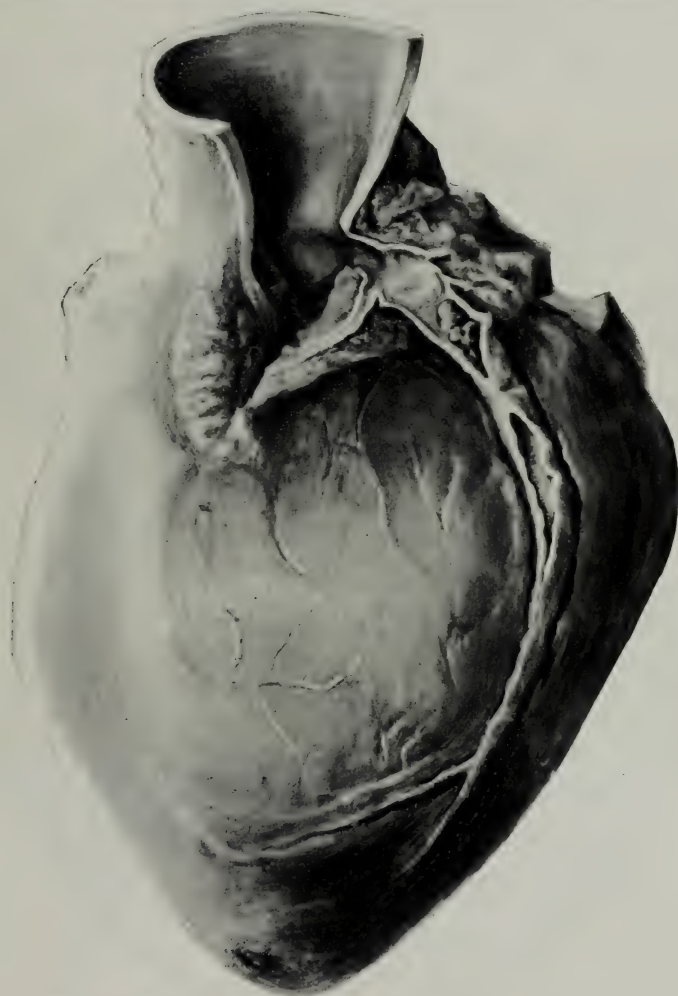


FIG. 204—Thrombosis of ramus descendens of left coronary artery.

permits of bulging of the ventricular cavity. If this project beyond the line of the epicardium, it constitutes an *aneurysm* of the heart wall; if it does not project outwardly, it is spoken of as a partial aneurysm. Probably because of nutrition derived from the blood in the chambers of the heart, either directly or through the Thebesian vessels (Pratt), there is practically always a narrow band of surviving myocardium between the base of the infarct and the endocardium. Early infarcts are not commonly accompanied by thrombosis in the chamber but after bulging occurs, thrombosis is almost constant. Histologic-

ally, the muscle shows first cloudy swelling, then necrosis which is hyaline or granular, followed by liquefaction and absorption. Fibrosis proceeds from preëxisting connective tissue and is similar to that of infarcts anywhere. Much has been written concerning regeneration of cardiac muscle, but in our

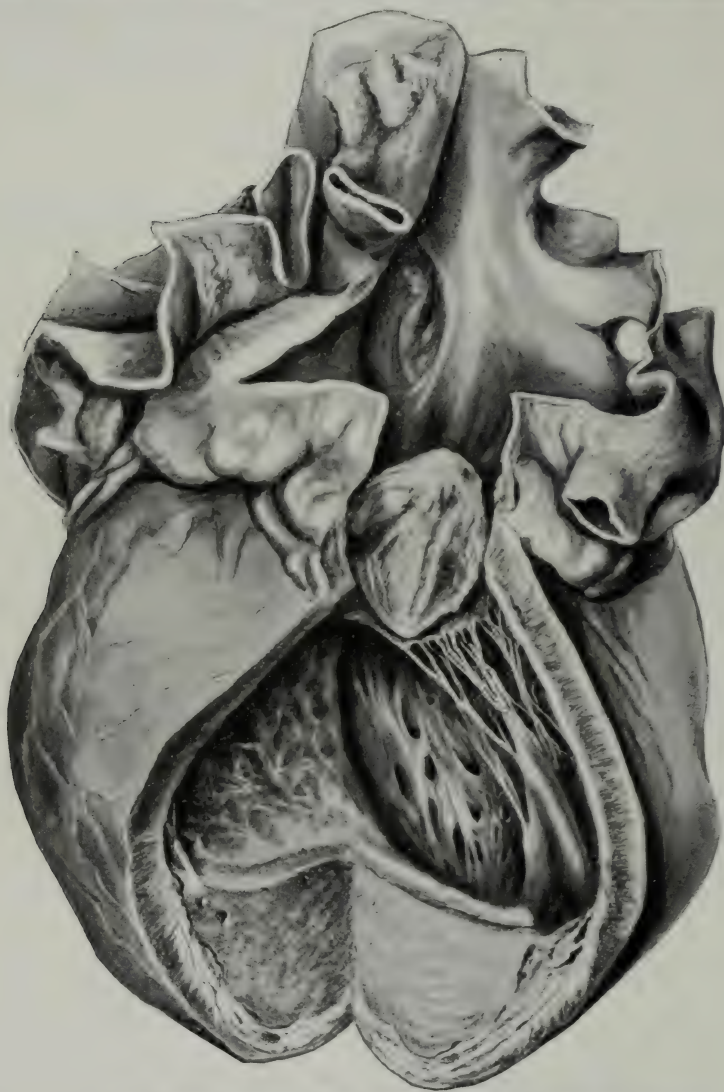


FIG. 205—Partial aneurysm of left ventricle due to old coronary occlusion. The apex of the left ventricle is thin and made up largely of scar tissue, and within the ventricle is a large mottled thrombus.

opinion no evidence has been adduced to support a hypothesis that it follows infarction.

Sclerosis of the coronaries may predispose to occlusion by emboli or thrombi. It is of great importance in leading to localized areas of atrophy of muscle and eventually to disappearance with a replacement fibrosis. Thus, numerous small scars appear, producing the so-called cicatricial or focalized

chronic interstitial myocarditis. This is progressive in so far as the underlying arteriosclerosis is progressive.

Functional Effects of Coronary Obstruction.—These are observed as immediate and more remote effects. In animals, experimental results are not constant, but Porter has enunciated the principle that the frequency of arrests of the heart is in proportion to the size of the artery obstructed. Miller and Matthews found that either main branch of the left coronary may be obstructed without serious effects. Obstruction of both the left circumflex and the ramus descendens practically always produces stoppage of the heart, the left ventricle ceasing to beat first. In our own experience, occlusion of either one of these branches is without serious immediate effects. Occlusion of the entire left coronary in Porter's hands led to rapid diminution of systolic, diastolic, and mean arterial pressure, terminating in stoppage of the heart. With the fall of blood pressure, there is a dilatation of the heart, which ultimately goes into ventricular fibrillation. Lewis found that occlusion of the right coronary leads to tachycardia. As Miller and Matthews have shown, the animal may survive the immediate process of ligation, as for example, of the ramus descendens, but if the area obstructed be large enough, death ensues from heart failure in from one to three months. Naturally, infarction occurs, but this is not a progressive process and apparently the heart muscle reaches a point where it



FIG. 206—Photomicrograph of hyaline and granular necrosis in experimental myocardial infarct of the dog.

can no longer stand the stress. Among the abnormalities of beat Herrick finds extrasystoles, tachycardia, auricular fibrillation, partial block, auricular flutter, and ventricular fibrillation. Electrocardiographic studies have been made by Smith in experimental animals and by Pardee and others in man. There is generally some disturbance of the T wave common to both animal and man. Pardee finds a disturbance of the Q, R, S waves in man. It may be said, however, that there is no constant electrocardiographic picture in this condition.

There can be no quantitative correlation between the effect of these lesions in animals and in man, because in the latter we deal as a rule with a heart whose muscle is otherwise diseased, usually in the form of a chronic interstitial myocarditis or even scars of previous infarcts, whereas in animals the heart muscle is normal. It would therefore seem likely that occlusion of the smaller branches in man, particularly when other cardiac disease is present, would be more serious than occlusion of comparable vessels in animals. Clinically, occlusion of

the coronary arteries may lead to immediate death without premonitory symptoms, or to death within a few minutes after onset with definite symptoms of heart failure. Nevertheless, patients may have serious symptoms clearly indicative of occlusion of the coronary arteries and yet recover (see Nathanson). In the event of recovery, it is possible that provided a considerable amount of one ventricular wall be thrown out of function, the opposite side of the heart may show definite preponderance in the electrocardiographic studies. This does not signify a hypertrophy of the opposite side. A diagnosis of coronary occlusion presupposes either arteriosclerosis with a secondary thrombosis or perhaps spasmodic contraction, or on the other hand, occlusion due to emboli, in which case a source of the embolus must be indicated.

Angina Pectoris is a clinical syndrome somewhat variable in character. Reid states that "typical angina pectoris is characterized by paroxysmal

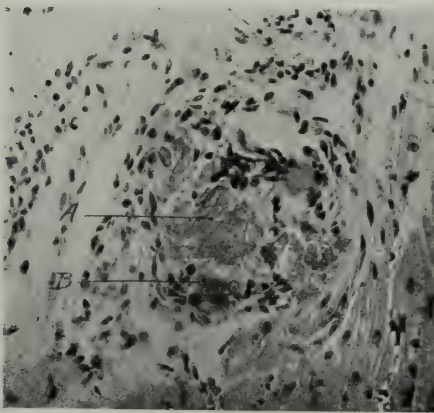


FIG. 207—Experimental myocardial infarct of the dog, showing at A necrotic muscle, and at B, foreign body giant cell as part of the process of organization.

attacks of pain over the sternum, often radiating to the shoulder and arm, and commonly associated with a sense of impending death." Numerous theories have been proposed to explain the symptoms, but none is finally proven. Albutt asserts that the condition is due to disease of the proximal part of the aorta. Hoover states that it may be due to "vascular crises in the coronary arterial distribution, due to vasomotor influences not associated with anatomical lesions of the arteries." These may be of reflex origin from numerous points of irritation or disease (Neusser).

The presence of vasomotor nerves in the coronaries is of significance in regard to this hypothesis (Wiggers). The influence of surgical operations upon the cervical sympathetic ganglia (see Penfield) may also be interpreted in the same way, but may be due merely to interruption of sensory impulses. The electrocardiogram shows no pathognomonic signs (Willins). In our experience, all the cases have shown coronary sclerosis, but numerous cases are reported without lesion in the coronaries, and many cases of coronary sclerosis do not have angina. Coronary sclerosis may exhibit symptoms like those of angina or a distinctly different clinical picture with pain, dyspnea, rapid heart rate or arrhythmia, etc. Askanazy describes a neuritis of the heart, but it may be said finally that there is no constant pathological anatomy of angina pectoris.

Acute Myocarditis.—This term is sometimes loosely employed, but to the pathologist indicates a condition in which there is, associated with muscle degeneration or necrosis, an infiltration into the interstitial tissues of cells usually found either in acute or subacute exudative processes. In the heart, a differentiation between acute parenchymatous and acute interstitial myo-

carditis does not seem justifiable. The lesion might be more properly referred to as an acute non-suppurative myocarditis. It is a common accompaniment of acute infectious disease, particularly diphtheria, scarlatina, typhoid fever, pneumonia, influenza, rheumatism, and septicemias or pyemias. It may also accompany exophthalmic goiter (Fahr) and certain other diseases. Experimentally, it has been produced by nicotine, alcohol, various digitalis preparations (Thalheimer), adrenalin (Loeb and Fleisher), and also adrenalin combined with spartein sulphate (Christian); uranium, arsenic, potassium bichromate (Walker) have been found to produce a slight myocarditis. Bacteria may also produce the lesion (Thalheimer and Rothschild). Goodpasture has produced degenerative and infiltrative lesions by the use of thyroxin and chloroform. There is little doubt that acute non-suppurative myocarditis may be associated with the presence of bacteria in the myocardium, but unquestionably the toxic materials produced by bacteria are of greater import. This is especially true of diphtheria, the toxin producing, according to Anitschkow, lesions essentially the same as those of man.

Grossly, the heart of acute myocarditis shows the soft, flabby, pallid, sometimes yellow, opaque muscle seen in cloudy swelling and fatty degeneration, but not infrequently in greater degrees. Microscopically, the muscle fibers show a variety of changes varying from simple cloudy swelling to fatty degeneration and granular and hyaline necrosis. Necrosis is often in small, irregularly disposed foci, about which the cellular infiltration may be greater than in other places. Sometimes vacuolar degeneration is seen. Except where necrosis is present, the nuclei show little change, except perhaps for slight pyknosis. The more



FIG. 208.—Low power photomicrograph of cicatrized myocardial infarct of the dog, showing triangular outline with base toward endocardium and layer of surviving muscle under endocardium.

severe degenerative changes are especially common in diphtheria (see Warthin). The cellular infiltrate of the interstitial tissue may consist of lymphocytes, leucocytes, plasma cells, and ultimately a growth of connective tissue. Inflammatory edema may be present and occasionally hemorrhage is encountered. Eosinophiles are likely to be rich in the acute myocarditis of diphtheria and also of acute tuberculosis. The foreign body type of giant cell is occasionally seen (Hafner). The myocarditis of acute articular rheumatism is likely to show, histologically, the presence of small clumps in the perivascular areas spoken of as the *Aschoff bodies*. These are composed of lymphocytes, plasma cells, and large mononuclear cells with a large vesicular nucleus, whose chromatin is likely to be centrally placed, with radiating lines extending to the nuclear membrane. Most authorities maintain that Aschoff bodies are pathognomonic of rheumatic myocarditis, but Lubarsch maintains that he has found them in cases that were not rheumatic. It is extremely difficult to state positively that a patient has not suffered a minor attack of

rheumatism. The Aschoff bodies can be identified for a long period of time after the acute attack of rheumatism has subsided, but ultimately may form merely small cicatricial areas in the neighborhood of myocardial blood vessels. Whitman and Eastlake maintain that the lesion is a local reaction to a small area of necrosis, and that many of the cells originate in the heart muscle fibers, but this view cannot be regarded as proven. The heart of acute myocarditis



FIG. 209—Chronic interstitial myocarditis, shown as gray streaks throughout the myocardium. There is also fresh necrosis of ventricular wall and papillary muscle due to coronary occlusion.

often dilates, and sometimes to such an extent that thrombosis occurs in the chambers of the heart either on the right or the left side.

Functionally, extreme weakness of the circulatory mechanism and various types of arrhythmia, such as described above in connection with degenerations may appear. Wiggers quotes certain authors as having described degenerative and infiltrative changes in the transmission bundles, which may explain certain cases of arrhythmia. Circulatory failure may be pronounced and, more especially in diphtheria, may lead to sudden death. MacCallum thought that circulatory failure in diphtheria is due to loss of vasomotor control, but Porter and Pratt determined that the vasomotor reaction is normal. This latter view is also supported by Marvin. Malcolm, supported by Henderson, offers the hypothesis that the infectious agent causes excessive passage of fluid into the tissues and thus reduces blood volume; the decreased return to the heart leads to a fall of blood pressure in spite of vasoconstriction. This may in part explain the efficacy of glucose as shown by Edmunds and Cooper.

Acute myocarditis may lead to death through circulatory failure because of direct influence upon the heart, or because of general circulatory disturbance. The patient

may recover and the end result be a chronic myocarditis. In young individuals many cases appear to result in complete recovery.

Chronic Interstitial Myocarditis.—This may be observed as a diffuse fibrosis of the myocardium or in a focalized form. The diffuse form is seen in those conditions where more or less widespread fibrosis of various organs of the body occurs. This is likely to be associated with chronic toxic processes such as chronic alcoholism, gout, lead poisoning, syphilis, tuberculosis, and is secondary to senile atrophies of parenchymatous tissues, and to arteriosclerosis. Since many of these causes may also produce increased resistance

to peripheral circulation, hypertrophy is a common accompaniment of the chronic myocarditis. Grossly, the heart is usually enlarged, and the muscle extremely firm. Tangential section of the myocardium shows a diffuse gray appearance such as is seen in tough beef.

The focalized form of myocarditis is usually cicatrical in character, following either small necroses incident to acute myocarditis, or either atrophy or necrosis of the myocardium due to diminished nutrition. Focalized atrophies are particularly likely to occur with arteriosclerosis of the coronary arteries. The fibrosis is patchy in character, appearing as small or large scars throughout the myocardium. Such areas are particularly likely to be seen in the left ventricle, more especially near the apex and in the septum, but may appear in the right ventricle or even in the atria. Here again, the general systemic

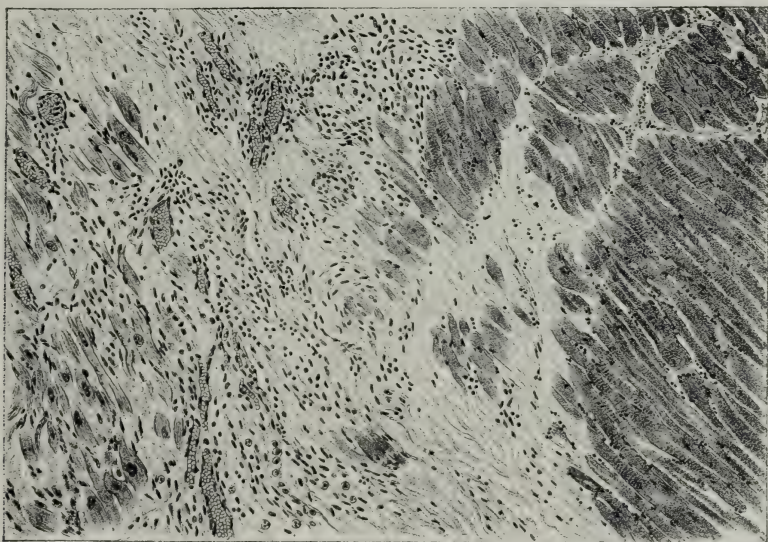


FIG. 210—Cicatrical type of chronic interstitial myocarditis.

disease may produce hypertrophy of the heart. It seems unlikely that hypertrophy occurs to compensate for the loss of active muscle substance.

Chronic diffuse myocarditis usually runs its course without any clear cut symptomatology. Occasionally, however, it appears to produce weakness of the circulatory apparatus and sometimes arrhythmia. This is true also of the smaller focal lesions. The larger focal lesions have already been discussed under the topic of infarction of the heart.

Acute Suppurative Myocarditis.—This is usually referred to as abscess of the myocardium. It is most commonly a part of a pyemia or septicemia, although it may be a direct extension from acute valvulitis or suppurative pericarditis. Streptococci, staphylococci, pneumococci, gonococci (rarely—Councilman) may be recovered. The abscesses are likely to be multiple with a diameter of only 2 to 3 mm. and surrounded by a zone of hyperemia or hemorrhage. They occur most commonly in the lower three-fourths of the left

ventricle, especially in the subepicardial muscle, and in the papillary muscles. Large, infected emboli may produce infected infarcts. Histologically, there may be a centrum of necrotic tissue, often containing a bacterial mass, surrounded by the usual cells of the abscess, or the cells infiltrate the necrotic area to produce the typical, focalized collection of pus. Rarely, healing occurs with cicatrization, but as a rule the patients die of the underlying septicemia or pyemia. Possible complications include extension to produce acute pericarditis, rupture of papillary muscle with valvular insufficiency, ulceration into endocardium with possible subsequent embolism.

Granulomata.—The most important are syphilis and tuberculosis, although others such as actinomycosis may occur. Syphilitic lesions may be either gumma or a diffuse chronic interstitial myocarditis. According to Warthin, the latter is extremely common in late syphilis. It may appear as a more or less diffuse infiltrate of lymphoid and other mononuclear cells, as a loose edematous or mucoid connective tissue growth, or as a dense fibrosis, associated with degeneration of the muscle. Special methods demonstrate the spirochete *pallidum*. Gummata may rarely be found in congenital syphilis, but are more common in acquired syphilis. They usually appear near the base of the heart, in the left ventricle or the septum. In the latter situation they may interrupt the conduction system, with consequent heart block.

Tuberculosis of the myocardium is rare. It may extend from tuberculous pericarditis, be a part of disseminated miliary tuberculosis or occur as conglomerate tubercles, especially in connection with massive tuberculosis of the mediastinal lymph nodes.

Abnormalities of the Size of the Heart.—The heart may be small because of hypoplasia. In this condition, the heart is small in all dimensions but otherwise normal. As compared with the normal weight of approximately 250 grams in women and 300 grams in men, the heart of hypoplasia frequently weighs as little as 200 grams. It is likely to be associated with hypoplasia of the arterial system generally, and may be found in status thymolymphaticus and in chlorosis.

Atrophy signifies acquired reduction in size of a heart. It is associated with wasting diseases such as chronic tuberculosis and malignant tumors. It commonly forms a part also of the general wasting of senility. Cardiac atrophy, therefore, may be nutritional or senile. The heart may weigh 200 grams or less. The reduction in size is due to atrophy in the muscle elements, which affects all diameters of the muscle fiber cell. The nuclei may or may not be reduced in size and are increased in number. The connective tissue and the arteries do not undergo similar reduction, nor does the normal pigment of the heart. The heart, therefore, shows general reduction in size, with tortuosity of the coronary vessels. Since the connective tissue remains normal in amount, the muscle is likely to be dense and of gray color. Because of the nature of the underlying condition, the fat of the epicardium also undergoes atrophy, and in the grooves of the heart the epicardium is wrinkled and the fat is a soft, gelatinous looking, dark yellow or orange material, so-called serous

atrophy of fat. The color of the muscle, especially in young individuals, is fairly normal, and the condition is spoken of as simple atrophy. More particularly in older individuals, brown atrophy occurs. In this condition the muscle is of deep brown color. As Dolley has shown, the pigment of the heart is made up in part of ingested lipochrome, but there is also a permanent granular brown pigment probably due to metabolic activity of the muscle, which increases as age advances. With normal hearts this pigment makes no important difference in the color grossly, but if atrophy appear, it is possible that the relative increase in pigment is sufficient to produce the deep color. Dolley maintains that there is also an absolute increase in amount of pigment. The atrophic heart is usually adequate to meet the mode of life of the individual, but certainly shows a decrease in reserve power.

Increase in Size.—The heart may be increased in general size because of hypertrophy or dilatation or both. *Hypertrophy of the heart* represents an adaptation of the heart muscle to meet increased functional demands. This presupposes a supply of nutrition adequate to permit of increase in bulk of the muscle. The work of the heart may be increased by added peripheral circulatory resistance, by conditions which demand an increase in pressure within the chambers to overcome circulatory resistance, or by conditions which necessitate an increased tonicity of the heart in diastasis. We may refer these etiological factors, therefore, to conditions within the heart itself, conditions in the general circulation, conditions in the pulmonary circulation and perhaps also to intrinsic or extrinsic nervous influences.

The most significant causative lesion in the pericardium is chronic adhesive pericarditis, either with or without chronic inflammation outside the pericardium. If the latter condition be present, it increases the attachment of the parietal pericardium to surrounding structures. Without the external adhesion, the normal attachments of the pericardium to the diaphragm, the hiluses of the lung, the cervical fascias and the anterior mediastinal ligaments, are sufficiently dense, so that when the sac is partly or completely obliterated, systole must occur against the resistance of these attachments. Certain authorities insist that there must be external inflammatory adhesions, but we have rarely failed to see hypertrophy in extensive pericardial adhesion regardless of external conditions. Extensive calcareous infiltration of the pericardium may reduce the elasticity of this structure to such an extent, that resistance is opposed to contraction of the muscle.

Certain authorities maintain that lesions in the myocardium, particularly healed infarcts or chronic interstitial myocarditis, may lead to a compensatory hypertrophy of the remaining muscle. This conception, however, is regarded with scepticism in view of the fact that such lesions are associated with general and local conditions, which are likely to interfere with nutrition of the muscle. Similarly, the theory that a myocardium, the seat of degeneration, may undergo hypertrophy to compensate for the poor ventricular contraction incident to the degeneration, is probably incorrect because of the presumptive inability of the degenerate muscle to take up the necessary additional nutrition.

The lesions of the endocardium of importance are particularly chronic valvular disease. While it is possible that subacute valvular disease may lead to hypertrophy, it seems likely that in this condition and in acute endocarditis, the associated intoxication of the general organism does not provide suitable conditions either for the supply of added nourishment to the heart, or the taking up of this supply by muscle which is degenerate because of the general intoxication. The stresses thrown upon the heart by valvular insufficiency and stenosis have been discussed in connection with chronic valvular disease. Not all valvular disease, however, produces notable hypertrophy of the heart, this being particularly true of mitral regurgitation. Particular valve lesions may lead to hypertrophy, predominantly in one blood chamber or on one side of the heart. This is associated with a slighter degree of hypertrophy of other chambers, because of the spiral arrangement of the muscles. Such hypertrophies occur without any general circulatory disturbance. The degree of hypertrophy of a given chamber can only be estimated by dissection of the heart along some such plan as that suggested by Lewis.

A most common cause of increased work of the heart is increased arterial pressure. Good usage permits the hybrid term hypertension, and relatively few employ the term *hypertonus*. Alburt suggests the use of *hyperpiesis* to indicate a hypertonus of indefinite origin, and *hyperpiesia* to indicate hypertonus secondary to some such lesion as chronic nephritis. It is probable, however, that these terms are inadequate, for the first probably includes two types of case and the second several types. If the work of Müller and Hübener be supported, *hyperpiesis*, or as it is commonly called, essential hypertension, comprises two groups. In the one there is a constitutional anomaly of arterioles and arteriolar capillaries, in which they are more tortuous than normal and probably more susceptible to prolonged vasoneurotic cramp. In the other, there is a fibrotic and degenerative lesion of the arterioles and arteriolar capillaries, which will be described in the section on diseases of arteries. This arterio-capillary fibrosis of Gull and Sutton, arteriolosclerosis of Jores and diffuse hyperplastic sclerosis of Evans (see also Fishberg) must affect at least a majority of the finer vessels before dilatation of other similar vessels fails to compensate. It is probable that those forms of presumably hereditary hypertension (O'Hare et al.) belong in the first group. Arteriosclerosis of the larger vessels, as well as aneurysm (except arteriovenous communications) do not of themselves produce hypertonus. Hypertonus may be secondary to chronic glomerulonephritis and to certain other conditions, including occasional cases of tumors of the adrenal (Oppenheimer and Fishberg). Arteriolar nephrosclerosis is not a cause but an incidental finding in hypertonus. How chronic nephritis operates to produce hypertonus is not known, but will be discussed in the chapter on the urinary system. As pointed out in the chapter on disturbances of circulation, an increase of circulating fluid causes an enlargement of the vascular bed, including the heart, and especially in connection with arteriovenous communications, is associated with hypertrophy. The so-called beer drinker's cardiac hypertrophy is probably not due to increased amount of circulating

fluid, because that is readily reduced, but is due to other influences, perhaps the alcohol. There has been much discussion about the influence of athletic sports and of hard muscular work upon hypertrophy of the heart. Certain clinical studies support the view that athletics and hard work produce hypertrophy of the heart and others contradict this view. Although the weight of the heart is likely to be more or less parallel to the amount of skeletal muscle, there is no satisfactory evidence adduced by postmortem examination of the heart to show that athletics or hard muscular work produces a true hypertrophy.

Numerous conditions in the chest may induce resistance in the pulmonic circuit. These include chronic diseases of the lung, such as chronic tuberculosis, emphysema, bronchiectasis, and extensive organized pneumonia. Much the same influence is exerted by conditions in the pleura which compress the lung, such as prolonged pleural effusion, empyema, pneumothorax and tumors of the pleura. Tumors of the mediastinum or aneurysm may also interfere with pulmonary circulation. Although pulmonary arteriosclerosis commonly accompanies hypertrophy of the right ventricle, there is no good reason for assuming that it plays any part in producing the hypertrophy.

Hypertrophy of the heart sometimes occurs in exophthalmic goiter, but whether this is due to nervous excitation producing tachycardia or to toxic disturbances is as yet not clearly shown. Paroxysmal tachycardia may also be associated with hypertrophy, but again it is not clear that the tachycardia itself is the cause of hypertrophy, and we have observed it in an atrophic heart. That drugs which increase the rate of the heart, such as alcohol, nicotine, coffee and others lead to hypertrophy is open to question, and even if such hypertrophy be demonstrated it is not clearly proven that the hypertrophy is due to the rapid rate.

Morbid Anatomy.—The chief criterion of hypertrophy of the heart is increase in weight. The thickness of the walls cannot be depended upon for diagnosis, because dilatation may thin the wall of a hypertrophic heart to a measurement less than normal, and stoppage in systole may result in a wall thicker than normal. Arbitrarily, a heart 600 grams or more in weight is called *cor bovinum*, or ox heart. The muscle of hypertrophy is firm and of more reddish tinge than normal. Fibrosis, a common accompaniment, increases and degenerations decrease the firmness. The papillary muscles and columnæ carneæ are large and rotund. The chambers are often enlarged, constituting the so-called eccentric hypertrophy. If the chambers be smaller than normal, the condition is often called concentric hypertrophy, but it is probable that this is due solely to stopping of the heart in systole. Most hypertrophies show enlarged chambers, but where the enlargement is marked there is an associated dilatation. The valve leaflets, more especially of the left side, are often sclerotic, and the neighboring mural endocardium thick and opaque. The coronary arteries are elongated in accord with the size of the heart and often increased in transverse diameter to accomodate the increased blood flow.

Microscopically, the muscle fibers are increased in transverse diameter and in length. As the process advances, the transverse diameters approach uni-

formity, presumably because all the fibers reach their limit of hypertrophy (Karsner, Saphir and Todd). The nuclei are not increased in number but are enlarged and show squared ends. There is often an increase in supporting connective tissue.

Hypertrophy compensates for increased resistance and operates so as to maintain a circulation of blood adequate to body needs. The reserve power of such hearts is not as great as normal. There is, however, a limit to which hypertrophy can progress and when this is reached, provided the increased demand for work continues, dilatation ensues, often with degenerative changes in the muscle in part due to inadequate nutrition. What determines the limitation of hypertrophy is not definitely known, but there are certainly limits to the growth of individual animal cells and there are presumably limits of the nutrition which may be provided. Up to the limit of hypertrophy, circulation is adequately maintained and the heart is said to compensate, but when the limit is reached and dilatation follows the heart is in a state of decompensation, or congestive failure.

Dilatation of the Heart.—Dilatation of the heart occurs when the muscle power of the myocardium is no longer sufficient completely to expel the blood in systole, and to maintain adequate tonus in diastole or diastasis. Normally the heart shows little alteration of volume except for the accommodation of variations in blood volume, as discussed in the chapter on disturbances of circulation. Passive or secondary dilatation of this sort does not presuppose a diseased muscle, and similar dilatations such as are supposed to occur in the early stages of chronic valvular disease may, because of increased tension upon the muscle, stimulate stronger contractions and subsequent hypertrophy. Transient secondary dilatations of any sort, including that sometimes observed in athletes, are readily recovered from. Active or primary dilatation of the heart is that form due to disease of the muscle, including the degenerative effects of infectious diseases, local or general anemias, embolism or thrombosis of the coronary arteries. These are of especial significance where the normal reserve of the heart is relatively reduced as in hypertrophy. The chamber or side of the heart upon which especial stresses are thrown may show predominant dilatation. Thus, in mitral stenosis, the left atrium may be the special seat of dilatation. In conditions where the systemic circulation throws great strain upon the heart, the left ventricle may be the seat of dilatation. Where right sided hypertrophy has occurred, the right side of the heart is likely to be dilated. Right sided dilatation is especially likely in pneumonia where there is not only increased resistance to pulmonary circulation, but in addition an important toxic factor which operates upon the entire heart but shows its effect principally upon the right side. Other conditions not interfering, the right atrium is the chamber which is most commonly dilated and dilated to the greatest degree. It is difficult to classify the dilatation which occurs when hypertrophy reaches its limit, for often there is no demonstrable degeneration of the muscle, but it is reasonable to suppose that a functional degeneration occurs, even though it be not demonstrated anatomically.

The dilated heart is enlarged and usually of globular form. In secondary forms the muscle is soft, flabby and dark red. In primary forms the muscle shows various types of degeneration, anemia or necrosis. The chambers are enlarged as indicated above. In the ventricles the especial feature of dilatation is flattening of the columnæ carneæ and papillary muscles. Microscopically the muscle fibers are narrowed because of attenuation. The nuclei may share in the attenuation. There may be no notable degenerative change in the muscle or there may be cloudy swelling, fatty degeneration or necrosis. The principle effects of dilatation are fall in mean systemic pressure and in pulse pressure, associated with passive hyperemia of the viscera, with all the attendant changes incident to passive hyperemia, both functional and morphological. The passive hyperemia has anatomically as its important sequels not only stagnation of blood in the vessels but edema, pigmentation, hemorrhage, parenchymatous degeneration, catarrhal inflammation and fibrosis. These may all give symptoms and signs referable to particular regions. Thus, there may be edema and bronchitis in the pulmonary area. There may be digestive disturbances due to changes in the various digestive glands. There may be disturbances of renal function somewhat resembling nephritis. Cardiac edema has already been

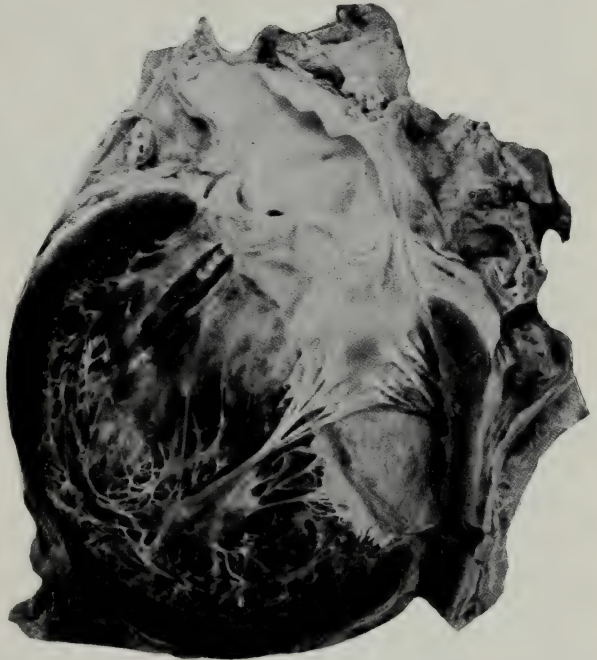


FIG. 211—Dilated heart with enlargement of chamber and flattening of columnæ carneæ and of papillary muscles. Note also the anomalous cord-like fibrous trabeculæ.

discussed in the chapter on disturbances of the circulation. Of great physiological importance are cardiac cyanosis and cardiac dyspnea.

Cyanosis.—The blue tinge of skin and certain mucous membranes is an important sign of cardiac decompensation. Of importance in explaining this type of cyanosis is the fact that capillaries, particularly in the lungs, are widely distended with blood and according to the studies of Stewart and Hewlett, the systemic circulation is slowed. In addition the lungs are likely to show various degrees of edema. The slowed pulmonary circulation, the dilated capillaries and the presence of fluid within the alveoli all operate to reduce interchange of gases. If the hyperemia be prolonged, fibrosis of the alveolar walls may occur with further interference with interchange. As Hoover has suggested, the presence of fluid interferes more with the taking up of oxygen than with dis-

charge of carbon dioxide but, nevertheless, there is an increase of carbon dioxide in the systemic blood so that the mean level of oxygen unsaturation of the capillary blood is elevated sufficiently to produce the cyanosis (see Lunds-gaard and Van Slyke).

Dyspnea.—The shortness of breath of cardiac decompensation is sometimes extremely severe. Several important factors probably play a part in this phenomenon. There is both clinically, as shown by Pratt and others, and experimentally, as shown by Drinker, Peabody and Blumgart, a considerable reduction in vital capacity. The experimental studies indicate that this is principally due to edema in the alveoli, but it is probable also that enlargement of the capillary bed and possibly fibrosis of the lung, as well as catarrh of the smaller bronchioles contribute an important part. The systemic factors contributing to cyanosis also operate in aiding in the production of dyspnea. In addition to the oxygen unsaturation of the blood, it is possible that there is reduced flow through the respiratory center. Acid intoxication has been demonstrated by Lewis and his coworkers, but it is at least possible that this is not entirely due to cardiac decompensation but is contributed to by the presence of nephritis or other disease. It is well known that patients suffering from cardiac decompensation cannot breathe as well in the lying as in the sitting posture. This is spoken of as orthopnea. Numerous explanations have been advanced but it appears to us that the most satisfactory is that of Christie and Beams. They find that in normal individuals there is an absolute reduction in the vital capacity in the lying posture. This absolute reduction is essentially the same for cardiac patients who suffer with orthopnea “of necessity,” but relatively and proportionally represents for these patients a much greater reduction. Their vital capacity is so greatly reduced by the disease that the additional reduction in the lying posture is sufficient to cause considerably greater discomfort. Cardiac asthma is probably produced by a sudden operation of any or all of the factors enumerated above. It is also possible that these conditions may contribute to, or be augmented by, spasm of the bronchiolar and bronchial muscle (see Means).

Alterations of Position of the Heart.—These may occur from congenital conditions already referred to or from pathological conditions in the heart itself in various types of hypertrophy or dilatation. Tumors of the chest, pleural exudates, intrathoracic adhesions, curvature or angulation of the spine, may push or pull the heart out of normal position. Distension of the abdomen by pregnancy, ascites, tumors, distension of gut by gas, may elevate the diaphragm and move the heart into a transverse position. Bodily habitus as in long narrow or broad short torsos, studied by Mills, may show the heart in more vertical or more transverse position. Larimore finds these differences associated with moderate or slight differences of blood pressure, but whether this is due to position of the heart or the general constitution is not yet determined.

Rupture of the Heart.—As pointed out by Krumbhaar and Crowell, most cases of spontaneous rupture of the heart are due primarily to coronary disease, which may produce numerous minute areas of fibrosis, may produce

infarction and partial or complete aneurysm. Death in these cases is usually due to hemopericardium. Rarely, if ever, does either degeneration or abscess lead to rupture. Traumatic injury of the heart may be of little direct significance if small, may lead to death from hemopericardium, or if the pericardium be sufficiently torn, from acute anemia. Infection from such wounds is usually confined to the pericardium but may involve the myocardium.

Tumors of the Myocardium.—Those of the endocardium and pericardium have been discussed. Kaufmann mentions among benign tumors the occurrence of fibroma, angioma, lipoma, leiomyoma, and particularly myxoma which is likely to occur in the left atrium and often is covered by a thrombus. Rhabdomyoma occurs as single or multiple tumors, probably congenital in origin. It is likely to be accompanied by tuberous sclerosis of the brain. Sarcoma may also originate in the myocardium (Beck and Thatcher). Primary tumors of the myocardium are rare. Metastatic sarcoma is not uncommon but secondary carcinoma is more unusual, occurring particularly in carcinomatosis. Melanoma metastasizes to the heart in a considerable percentage of the cases. Direct invasion of the peri- and myocardium may follow cancers of esophagus, lung, thymus and the mediastinal lymph nodes. Leucemia may show diffuse or focal infiltration of the myocardium.



FIG. 212—Multiple metastases of melanoma of skin to myocardium, with projection into pericardium.

Parasites.—*Echinococcus* cysts and indeed other cysticerci may appear in the myocardium. The former may attain considerable size and lead even to rupture of the heart.

Foreign bodies, particularly metallic objects such as shot and needles sometimes enter the heart apparently by transport in the circulation, or in the case of needles by direct wandering in the body.

Cardiac Arrhythmias.—This field is so large and is covered so admirably in texts on medicine as well as such special texts as those of Lewis, Hirschfelder, Lamson, MacKenzie, Neuhof, Wiggers and others, that only the pathological basis of arrhythmias will be mentioned here. This pathological basis is both functional and morphological and is concerned particularly with irritability

and conductivity. Such alterations may be due to infectious or toxic agents which produce no lesion of the conduction system demonstrable by present histological methods and little change of significance in the myocardium. There may be tachycardia and bradycardia, sinus arrhythmias, atrial flutter and fibrillation, partial and complete heart block. Autopsy may show only acute or chronic myocarditis without lesion of the bundles and it is conceivable that such anatomical lesions may alter the irritability and conductivity of the myocardium, but how they operate is problematic. Acute degenerative and inflammatory lesions of the nodes and bundles are sometimes demonstrable. These may lead to increased excitability and perhaps to increased conductivity after the same fashion that acute inflammations produce increased nervous excitability. They may on the other hand be sufficiently destructive to produce depression or complete suppression of excitability and conductivity. Chronic inflammations are depressive. To the pathological anatomist, the most satisfactory field for study at present is in cases of partial or complete heart block. Wiggers states that lesions of the A-V node, bundle of His or its branches are frequently encountered and that "inflammatory reactions with edema, cellular infiltrations such as occur during rheumatic fever, influenza, typhoid, pneumonia and syphilis, septic foci, postinflammatory fibrosis, fatty and calcareous degenerations, ulcerations (from acute endocarditis), tumors and, by far the most frequent, gummata, have all been found in cases that succumbed to this condition." It is important to note that where such lesions are encountered in the conduction system postmortem, there has always been, in well studied cases, some manifestation of block. On the other hand, as emphasized by Krumbhaar, certain cases of block are characteristic clinically and show no demonstrable lesions postmortem either grossly or microscopically.

ARTERIES

Congenital Anomalies.—The evolution of the arteries is through such a series of developments and atrophies that frequent minor and major anomalies are to be expected. It is marvellous that they are not more common than they are found to be. Fetterolf describes anomalies in origin, position and branching of fifty arteries in a large anatomical material and this undoubtedly does not exhaust the list. Such alterations are of the utmost importance to the surgeon but are rarely of functional significance except by accident. The most important anomaly is patent ductus arteriosus, which may in early life be so wide as to cause mixture of blood. Minor patencies may be survived and produce no disturbance unless other altered relations produce a higher pressure in the pulmonic than in the systemic aorta. Transposition of the great vessels occurs with, or independently of, situs inversus viscerum and may be complete or partial (McMeans).

Hypoplasia of the aorta and larger vessels was described by Virchow. It is not infrequently associated with chlorosis but there is no proven etiological relation. The same is true of pernicious anemia, hemophilia, purpura, status thymolympathicus (Kaufmann). The aorta is not only reduced in size but

usually has an abnormally thin wall. The condition may apparently predispose to acute aortitis (Rolleston). The associated conditions and symptoms are discussed by Abbott.

In intrauterine and early life the arch and thoracic aorta may be separated by a slightly narrowed isthmus which usually disappears subsequently. This may persist or increase in degree producing the condition known as coarctation of the aorta. It may interpose sufficient resistance (stenosis) so that blood pressure is much elevated proximally, leading to dilatation and thinning of the arch, which in some instances may rupture with fatal results (Goldblatt).

Degenerations.—There is little doubt that toxic agents, infectious diseases and local inflammations may produce cloudy swelling of endothelium and of muscularis, and that the latter may have some physiological influence upon arterial tension, but the most significant of the degenerations from the viewpoint of pathological anatomy is fatty degeneration of the intima. This occurs commonly along the posterior wall of thoracic and abdominal aorta as slightly elevated yellow streaks one or two millimeters wide or as small nodules or plaques. It is seen usually in early life, especially accompanying a wide variety of acute infectious diseases. Histologically, the fat is in the form of minute droplets within the connective tissue cells, in tissue spaces and sometimes within phagocytes, the whole mass often constituting stellate figures. The sequence of this change is unknown, but it may possibly be a forerunner of arteriosclerosis. Fatty degeneration of the media of smaller arteries may be observed in many infectious diseases (Frothingham).

Pigmentation of the endothelium of smaller arterioles may be observed in malaria. Hyalin is particularly common in the central arterioles of the spleen, but occurs in numerous other small arteries and is seen in glomerular capillaries of the kidney in such acute infections as diphtheria and scarlatina. Amyloid is common in arterioles and capillaries as has been discussed in the section on degenerations.

Necrosis of the arteries is most common as a part of arteriosclerosis, but as the result of either toxic agents or acute infectious diseases, small necrotic areas may occur in either the media or intima. It is particularly common in the media as the result of syphilitic mesarteritis. It is said to occur also as the result of embolic or thrombotic occlusion of vasa vasorum.

Calcification is most common in the intima as a part of arteriosclerosis and may follow fatty degenerations, hyaline transformation and necrosis. It occurs in the media of middle sized arteries, more especially of the lower extremities, in old age. This is referred to as the senile or Mönckeberg type of arteriosclerosis, to be discussed subsequently. Calcification of the arteries also occurs as part of so-called metastatic calcification.

Atrophy occurs normally in the regression of arteries useful only in fetal life. It may be a part of senile changes. It occurs from disuse, as following amputations or occlusion.

Hypertrophy may occur in arteries which take over collateral circulation and as the result of the increased pressure of hypertension.

Acute Inflammation.—This is usually secondary to lesions elsewhere. Acute periarteritis occurs when local inflammation extends so as to involve the adventitia. It may extend further into the vessel and lead to rupture, unless circulation has been shunted by protective occluding thrombosis. The hemorrhage may be local producing a hematoma or false aneurysm, or the blood may pour into a cavity or on a body surface. Acute inflammation of the media and intima is commonest in small arteries, and is described especially in meningeal arteries in the course of various forms of acute meningitis. Acute inflammations primarily involving the intima are usually due to lodgment of infected emboli. These may occlude and subsequently produce abscesses or may result in mycotic aneurysms. Acute endarteritis of the aorta and pulmonary artery is usually the result of extension of an acute endocarditis from aortic or pulmonic leaflets. Embolism of the vasa vasorum may produce local suppuration in large vessels which may result in mycotic aneurysm or rupture. Such lesions may heal with scar formation.

Periarteritis Nodosa.—This is a rare, progressive inflammatory disease of smaller arteries, occurring at almost any period of life, affecting especially the renal, coronary, small abdominal, cerebral and other vessels. Its cause is unknown. Lemke inclines to the view that it is simply one variety of acute vascular inflammation that may also be manifested in other ways, and that it may be the sequence of a variety of infectious agents. Klotz emphasizes the importance of streptococci. Ophüls suggests rheumatic fever as a possible cause. Harris and Friedrichs, as the result of poorly controlled experiments, believe it to be due to a specific filter-passing organism. Syphilis is by no means constantly present, but may predispose to the disease (Klotz) or may produce a special variety (Dickson). Differences of opinion exist as to histogenesis but the scheme of Harris and Friedrichs is probably correct. They believe that the process is primary in the adventitia as an infiltration of inflammatory cells and even of fluid. According to Lemke it may also originate in the media. Extension of the process involves the media in inflammation and necrosis, with subsequent similar involvement of the intima. Aneurysms with or without thrombosis occur and small hemorrhages may produce false aneurysms; massive hemorrhage may also occur. The aneurysms and thrombosis lead to more or less extensive degenerations and necrosis of the parts supplied by the affected arteries. Grossly, the lesions appear as nodules varying in size from one to several millimeters, firm, pinkish-yellow or occasionally red in color, projecting along the course of the vessels and associated often with small hemorrhages, degenerations and infarcts. Dickson's term, *polyarteritis acuta nodosa*, is more descriptive than the generally used *periarteritis nodosa*.

Chronic Inflammations.—These include a variety of conditions the most frequent and important of which is the process called *arteriosclerosis*. Other names such as *atherosclerosis* have been applied and perhaps are in some respects more correct literally, but the term *arteriosclerosis* now enjoys widespread usage. Thorel defines *arteriosclerosis* in the broader sense as including all those pathological alterations of the arteries which lead to thickening of the

wall, particularly of the intima, and which in their development exhibit degenerative processes, such as fatty and mucoid degenerations, with their sequences. Included in Thorel's conception are calcification (also in the media), and in addition hyperplastic alteration of the connective tissue and elastic elements of the intima and perhaps also inflammatory proliferative growth of the connective tissue of the intima. All these are interrelated in a more or less complex fashion. Our primary consideration is of the so-called simple or intimal arteriosclerosis, which as will be seen subsequently is to be differentiated from other forms of chronic inflammatory arterial disease. The fundamental primary change is in the intima but its exact nature is not definitely known. Suggestions as to the nature of the earliest lesion include small tears of the elastica or connective tissue, fatty degeneration such as has been mentioned above, local degeneration or necrosis due to disease of the vasa vasorum, acute inflammatory lesions of the intima including fibrin formation, toxic necrosis of the intima or of its endothelium, and infiltration of lipoids. Under varying experimental and human conditions any of these lesions may be found, but it is

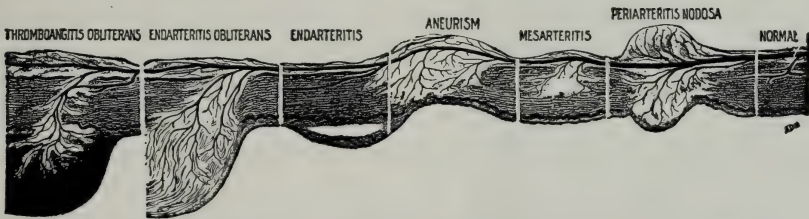


FIG. 213—Schematic drawing of various types of arterial lesions. From Hirschfelder, *Diseases of Heart and Aorta*.

extremely doubtful that any one has a universal application. We accept the assumption that the first lesion is damage in the lower intima with splitting of the elastic fibers, some destruction of fibrous connective tissue and even of muscle, and deposit of lipoids. In response to this injury connective tissue is formed in excess so as to produce intimal plaques. At the autopsy these plaques project into the lumen of the vessel, but that this is true in life is open to some question. This fibrous overgrowth is succeeded by hyalinization and, either before or coincident with hyalinization, there may be mucoid degeneration of the connective tissue. Grossly, the plaques now assume a pale blue translucent appearance, instead of a dull gray opaque appearance of the fibrous plaque. The next change commonly called atheroma is really a fatty necrosis of the thickened intima. The plaques now become yellow in color and soft in consistence. Microscopically, there are found fat globules, lipid globules and fatty acid and lipid crystals. By microchemical tests, of uncertain specificity, Klotz has found soaps, but this was not confirmed by Wells and others with more exact chemical methods. The necrotic area may become very much softened and the plaque appears as a fluctuating mass with semifluid, yellow, granular contents. This is sometimes incorrectly referred to as the atheromatous abscess. The superficial intima may become involved in the process and

slough, leaving the atheromatous ulcer which may serve as the basis of thrombus formation. Calcareous deposits occur either upon the hyaline material or



FIG. 214—Simple arteriosclerosis, showing fibrous and hyaline plaques, atheroma, and at the bifurcation, stiffening by calcification. Army Medical Museum 13121.

within the atheromatous areas and occasionally may be succeeded by true ossification. Calcified plaques may also project through the intima and produce marked roughening of the wall of the vessel with possible thrombus formation.

Affecting the aorta, the condition is likely to extend throughout the entire length of the vessel, with the more advanced lesions in the abdominal portion near the bifurcation. Affecting medium sized or small arteries, the same condition may produce the type of lesion now commonly called endarteritis deformans, in which the lumen is deformed by the projecting plaques, or produce endarteritis obliterans in which the plaque formation entirely occludes the vessel. These terms were first employed by Virchow to indicate the condition in any situation, but are now usually limited to the lesion as it affects the medium sized and small vessels. As a rule, the disease in the aorta is accompanied by similar lesions in smaller vessels, but this is not necessarily the case. The process may be confined to coronary vessels, to renal vessels, to cerebral vessels without being accompanied by any serious lesion of the aorta, and vice versa.

The cause of arteriosclerosis is obscure. In variable degrees it is nearly always present in the aortas of individuals thirty years or more of age. It sometimes occurs in very early life. It is unlikely, however, that age in itself is to be regarded as a definite cause, as it is not uncommon to find individuals sixty years old or more with relatively little arteriosclerosis. Age, however, emphasizes that vague phenomenon spoken of as the wear and tear of life, but if this be analyzed, there are numerous conditions which probably have an effect such as acute and chronic infectious

diseases, the use of improper food, the consumption of poisonous substances and hard physical and mental work. Although the disease may occur in members of the same family through several generations, there is serious doubt that this is due to heredity in the true sense of the word, but more probably because the same habits of life are passed on through generations. Osler lays considerable emphasis upon the inherent capacity of arteries to withstand stresses and strains, but it cannot be demonstrated that this assumption has definite anatomical or physiological foundation. It is sometimes thought that those who perform hard physical labor are more susceptible to arteriosclerosis, but it must be recognized that at the same time these individuals are likely to be subjected to other vicissitudes of life, and it is seriously to be questioned that the work itself is of importance except perhaps as a contributing factor, through the medium of improper eating, rapid metabolism (see Saphir), increased metabolic wastes, etc. The influence of various drugs has been extensively studied but without producing convincing results. Thus tea, coffee, nicotine, lead and other substances are said by certain investigators to produce the lesion experimentally, but this is not uniformly confirmed. Similar doubt exists in regard to the etiological relationship of such chronic diseases as gout, chronic muscular rheumatism, chronic nephritis, diabetes, obesity, etc.

The relation of acute infectious diseases to arteriosclerosis has been carefully studied and there is much reason for believing that various types of damage occur to the arterial system during the course of acute infectious disease, particularly rheumatism, typhoid fever, scarlet fever, diphtheria, and influenza. The damage varies from disturbance of the lining endothelium to fatty degeneration of various parts of the vascular tree, and even necrosis of intima and media have been described. The incidence of acute infection is so great that it is difficult to reach a final and positive conclusion as to relationship. Nevertheless, the known arterial changes which might be followed very readily by the inflammatory, destructive and reparative processes of arteriosclerosis, makes it highly probable that this sequence of events occurs.

There remains for consideration the relationship between high blood pressure and arteriosclerosis. The coincidence of these two conditions clinically is not uncommon, but the simple fact that many cases which clinically show extremely high systolic pressure and relatively little arteriosclerosis of the larger vessels, makes a necessary relationship between the two highly improbable. Klotz produced sclerotic lesions of the vessels of the head and neck of rabbits by suspending them upside down for half an hour every day over a long period of time. The lesion, however, was not constant in all the animals and other investigators have failed to obtain the same results. The resistance of arteries to extremely high internal pressure is truly remarkable, and we have failed to find any evidence of injury to the carotid artery of the dog after submitting it to internal hydrostatic pressures of 360 mm. of mercury. It seems unlikely that the pressures which occur in life can produce definite damage to these tubes. On the other hand, if disease be already present it is possible that high tension may produce slight lesions which favor the progress of the disease.

Adrenalin has been used by numerous workers for the production of arteriosclerosis in the rabbit. It is obvious, however, that this does not maintain a prolonged elevation of blood pressure, and the work of Pearce would indicate that this sclerotic lesion is the result not of the high blood pressure itself but of degenerative and hemorrhagic lesions in the vessels.

A great deal of experimental work has been done recently with the use of cholesterol given in the food, and it is found that this produces a rich infiltrate of lipoids into the arterial intima, as well as into other situations, with arteriosclerosis. The arteriosclerosis so produced is not strictly like that seen in man but probably approaches it more nearly than any other experimental form. Newberg produced fairly characteristic lesions by the use of high protein diet in rabbits and suggests that the effects attributed to cholesterol may be in part due to the protein factor. Various bacterial extracts and poisons have been employed, but do not produce a lesion that is strictly comparable to that in man.

In summary, it would seem that arteriosclerosis results from the presence of unknown toxic substances either of endogenous or exogenous origin, the most important of which, until our exact knowledge of the etiology is extended, are those of the acute infectious diseases. This, however, does not explain the progressive character of the disease. We do not know whether the initial lesion develops after recovery from the infection, whether there must be repeated infections, or whether there must be an element of chronicity following the acute infection. It is probable that nutritional or toxic disturbances, either acute or chronic, which may produce degenerations elsewhere, also operate upon the arteries, and further that the accompanying degenerative arterial lesion requires more chronic toxic or metabolic derangement in order for the lesion to become progressive. The rôle of increased blood pressure, if any, has not been determined but it is possible that arterial disease may be augmented by this factor.

The functional disturbances associated with arteriosclerosis depend upon the extent of the lesion and the character of the vessels affected. There is no good reason for believing that arteriosclerosis of the larger arteries has any serious influence upon blood pressure, although the stiffening of the larger tubes may throw additional work upon the heart. If, however, similar lesions are found within the arterioles or the capillary ends of arterioles, the resistance to circulation may be so increased as to produce marked elevation in blood pressure. In the arterioles and smaller arteries of kidney and other organs, the reduction in size of lumen of the vessel may lead to atrophy of the area supplied. If this be accompanied by thrombosis, necrosis of the part may ensue. Osler and others have been of the opinion that sclerotic vessels supplying such important organs as heart and brain and perhaps other areas are more susceptible to spasmodic contraction than are normal vessels. There is little to support this point of view and it seems to us more likely that these vessels simply show the effect of spasm more markedly than do other vessels. This has been referred to in connection with angina pectoris. Affecting vessels of the brain, transient paralysis may result. Rarely, simple intimal arteriosclerosis may lead

to aneurysm of the aorta or of other vessels. It must be recognized that this discussion of arteriosclerosis is of greater brevity than the extent of investigations or the importance of the condition would indicate, and the reader is referred for further information to such admirable articles as those of Thorel, MacCallum, Osler, Ophüls, Jores and Faber.

Senile arteriosclerosis is often called Mönckeberg arteriosclerosis, although previous writers had described it. The early change is usually fatty degeneration of the middle layers of the musculature and elastica of the media, which may be associated with necrosis. There is then calcification in the same situation. This may be in small nodules or more commonly in partial or complete rings, which give the so-called "corduroy" artery, or continuous calcification by fusion of the rings producing the "pipestem" artery. Rarely, ossification is observed. The condition is common in old age and affects particularly such arteries as the femoral, radial, temporal and dorsalis pedis. Other than this the cause is not known. There is discussion as to whether or not it should be regarded as arteriosclerosis, but it is included in the general definition we have accepted. Thorel is of the opinion that it is not essentially different from intimal sclerosis. The intima of the affected arteries may or may not show some stage of sclerosis. This is in addition to that simple increase in thickness of intima which Thayer and Fabian have shown to accompany old age. Severe degrees of peripheral senile sclerosis may be associated with little sclerosis in the aorta. Medial calcification occurs in the aorta almost solely as an extension from intimal disease.

Endarteritis Obliterans or Deformans.—This has been referred to in discussing simple intimal arteriosclerosis and is the same disease in smaller vessels. The lesion, however, occurs in both its deforming and obliterating stages as a purely productive process with growth of connective tissue and without atheroma or calcification. The normal prototype of this condition is seen in the obliteration of umbilical and hypogastric arteries and ductus arteriosus. Similarly, the obliterated diseased artery becomes converted into a fibrous cord. Much the same appearance may be produced by organization of a thrombosed artery.

Diffuse Vascular Disease.—In explaining certain types of chronic kidney disease and of high blood pressure, a sclerotic process of the small arteries and arterioles has been described as the underlying process. The condition was noted in the last century and is often called arteriocapillary fibrosis of Gull and Sutton (1872). More recently important studies have been contributed by Jores, by Gaskell and by Evans, who proposes the name diffuse hyperplastic sclerosis. It is apparently a manifestation of arteriosclerosis affecting the small arteries and by no means confined to the kidney. It affects particularly the vessels of kidney, spleen and brain (especially meninges) but those of practically any organ may be so diseased, save only those of the myocardium and skeletal muscle. Microscopically, there is thickening of the intima due to fibrosis, distributed rather uniformly around the lumen and sometimes producing occlusion, but not necessarily extensive in the longitudinal diameter of

the vessel. Fatty degeneration of the intima is common, but with the special stains appears to be diffuse rather than in droplet form. The condition is commonly associated with the small granular kidney, and also with cerebral hemorrhage. Affecting many areas in the body, resistance to circulation is produced and vascular hypertension results as discussed above.

Thrombo-Angiitis Obliterans.—This is an inflammatory lesion of arteries and veins with both acute and chronic phases, probably of unknown infectious origin, occurring more especially in Polish, Galician and Russian Jews and attacking the lower more often than the upper extremities. According to Buerger's studies, it originates as a red thrombus in the vessel with marginal foci of leucocyte infiltration, often succeeded by "giant cell foci" resembling



FIG. 215—Syphilitic mesaortitis above aortic valves, showing hyaline plaques and retraction of intima, with thickening and retraction of valves.

miliary tubercles. Organization and canalization of the clot are accompanied by fibrosis of media, in which are also found occasional giant cell foci. The chronic inflammatory process of the vessel walls may involve surrounding tissues and accompanying nerve trunks. The disease may be progressive involving several extremities. Gangrene (infarction of the extremities) usually results.

Other diseases leading to necrosis of the extremities include endarteritis obliterans, either primary or as a complication of senile arteriosclerosis. Raynaud's disease which shows in the earlier stages temporary anemia of the parts or sometimes cyanosis (acro-asphyxia) often induced by exposure to cold, is probably due to spasm of the blood vessels, is not necessarily associated with definite morphological changes in the vessels and does not always lead to necrosis (see Osler). Gangrene associated with diabetes and ergotism are also due to vascular disturbances.

Syphilis.—Although gummata may occur in the arterial system and syphilis may indirectly cause simple intimal arteriosclerosis, the most characteristic lesion of the vascular system is syphilitic (luetie) mesaortitis. This is commonly regarded as a special form of arteriosclerosis. A relationship between syphilis and arterial disease has long been inferred and was noted by Lancisi in 1728, but the identity of this particular condition was established by Döhle in 1895, was rapidly followed by the confirmatory work of Heller and subsequently Marchand and others, and was studied in this country especially by Longcope, Pearce, Symmers, Cummer and Dexter, and numerous others. The lesion is essentially a perivascular infiltration of lymphoid cells in the media, with local destruction of elastica and muscle, followed by cicatrization and secondary effects upon the intima. It affects males much more commonly than females, usually occurs in the fourth and fifth decades of life and in untreated or neglected cases leads to death about twenty years after the initial infection. Warthin, however, has found the lesion within eighteen months of the primary infection. Symmers and Wallace conclude quite properly that the production of syphilitic aortitis "is favored by certain other factors among which age, sex, the length and character of antisiphilitic treatment, intercurrent disease, especially infections such as acute rheumatic arthritis, alcoholism, and occupations necessitating prolonged physical strain play a not unimportant rôle."

Anatomically the lesion is usually localized to the ascending aorta or the arch, but may be more extensive or localized in thoracic or abdominal portions. There are projecting patches of pale blue, translucent, hyalinized thickened intima with little or no atheroma or calcification. Within or between the patches there is retraction of the intima producing stellate or parallel depressed lines, due to contracting cicatrices in the media. Transverse section of the media may show the small foci of fibrosis. Due to interruption of muscularis and elastica, the affected part is usually dilated and in about 30 per cent. of the cases accompanied by aneurysm. Dilatation of the aortic ring is extremely common. In a certain number of the cases there is also involvement of the aortic leaflets with thickening and retraction (Scott). Microscopically, the intima shows fibrosis, hyalinization and, uncommonly, atheroma and calcifi-



FIG. 216—Syphilitic mesaortitis and dilatation of arch of aorta. Aortic valves are thickened and retracted and heart much dilated.

cation, corresponding to the gross appearance. The media shows irregularly disposed perivascular (vasa vasorum) collections of lymphoid and plasma cells. There is often a number of endothelial cells and occasionally when necrosis occurs the lesion resembles miliary gumma. Sometimes giant cells are observed. The muscularis and elastica are definitely interrupted by the lesion. Surrounding it is usually dense fibrous connective tissue in more or less stellate arrangement, often in association with retraction of the intima. The adventitia may be fibrosed and usually shows similar perivascular lymphoid and plasma cell infiltration. *Spironema pallidum* is often to be demonstrated within the lesion and in the nearby portions of the vessel. Klotz describes similar lesions in congenital syphilis.



FIG. 217—Photomicrographs of syphilitic mesaortitis showing at the right, the perivascular cellular infiltrate and at the left, interruption of elastica. From Hirschfelder, *Diseases of the Heart and Aorta*.

“The early symptoms and signs of syphilitic aortitis are a positive Wassermann reaction, precordial pain, slight dyspnea, attacks of paroxysmal dyspnea, angina pectoris, cardiac hypertrophy, increased pulsation of the vessels of the neck and signs of dilatation of the aorta” (Longcope). Physiologically, the effects are much the same as those of aortic arteriosclerosis, until aortic insufficiency due to dilatation of the ring or retraction of the leaflets supervenes. We have observed one case in which adhesion of the leaflets produced stenosis, a distinctly rare lesion. Aneurysm gives its own signs and symptoms.

Syphilis commonly affects the arteries of the base of the brain as described in 1874 by Huebner, producing thick, stiff, semitranslucent hyalinized vessels (“like cooked macaroni”). This is described further in the chapter on nervous system. Warthin finds that among syphilitics simple arteriosclerosis of such

arteries as the renal, splenic, mesenteric, prostatic, coronary and cerebral arteries, is twenty-five times as common as among non-syphilitics. He finds definite syphilitic mesarteritis in carotids, subclavians, iliaes, femorals and pulmonary arteries, usually of slight degree and only demonstrable microscopically, but occasionally grossly visible and even with aneurysm formation.

Tuberculosis of the arteries may occur primarily as a tuberculous periarteritis or as a tuberculous endarteritis. The former is common as the result of extension of a tuberculous lesion where the adventitia is first affected, followed by subacute or chronic inflammation of the entire wall and thrombotic occlusion of the vessel. It becomes converted into a fibrous cord and forms some of the trabeculae in tuberculous cavities of the lungs. It may, however, lead to such weakening of the wall with or without the formation of aneurysms, that rupture occurs. Similar aneurysms of the aorta are reported as the result of tuberculous mediastinal lymph nodes. These aneurysms differ from those of syphilis in that the latter are due to stretching of a cicatrized wall rather than a wall part of which is destroyed by inflammatory destruction as in tuberculosis. Extension of the lesion into arteries may discharge bacilli into the blood stream with a consequent disseminated miliary tuberculosis. In cerebral and other similar arteries infarction may follow occlusion. Tuberculous endarteritis is rare but has been observed in the aorta upon either normal or sclerosed intima. It is characterized by the appearance of miliary or small conglomerate tubercles. The lesion may be seen in medium sized arteries. It is more likely to be an accompaniment of, than a cause of disseminated miliary tuberculosis.

Aneurysms.—An aneurysm is a permanent dilatation of an artery due to alteration of its wall. Two great divisions are recognized, namely true aneurysms and false or spurious aneurysms. The former group includes primary or spontaneous aneurysms, traumatic, dissecting, embolic and erosive aneurysms. False aneurysms are usually due to traumatic rupture of the vessel wall and the consequent formation of an encapsulated hematoma communicating with the original vessel. Most of the cases of arteriovenous communication are of this sort. Occasional cases of congenital aneurysms occurring in the ductus arteriosus and other situations have been reported.

Primary or spontaneous aneurysms are given names according to their form and may therefore be fusiform, cylindrical, saccular or cirroid. Such conditions may affect a variety of arteries, but the diffuse (i.e. fusiform or cylindrical) and saccular forms are most common in the aorta. The cirroid aneurysm is distinctly more common in the smaller vessels such as the temporal arteries, where there is a general dilatation associated with lengthening and tortuosity. The primary condition in these forms of aneurysms is some variety of arteriosclerosis. In the aorta, by far the commonest primary disease of the vessel is syphilitic mesaortitis. We have observed only a few cases of diffuse and of saccular aneurysms of the aorta due to simple arteriosclerosis. The fundamental and underlying condition essential for the production of such aneurysms is disease of the media of the aorta, since this part of the wall offers the main

support against the internal distending pressure. This is easily understood in the case of syphilitic mesaortitis, and in simple arteriosclerosis is almost certainly due to extension of the process from the intima into the media, with interruption of elastica and muscularis. The site of such aneurysms is usually in the ascending aorta or the arch. They may also occur in the thoracic and in the abdominal aorta. Indeed, multiple aneurysms involving various parts of

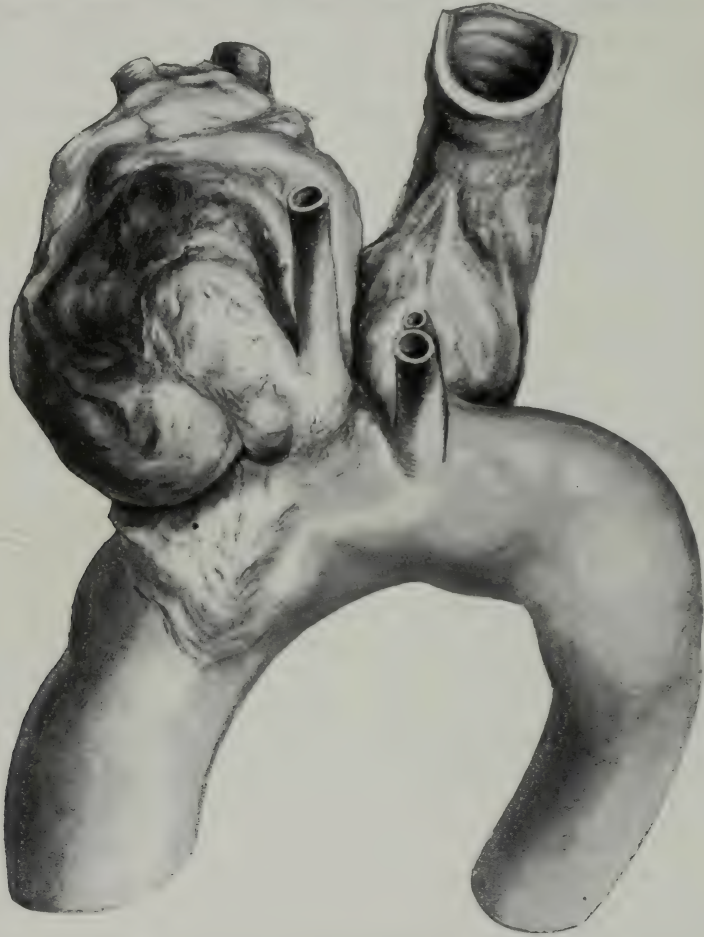


FIG. 218—Saccular aneurysm of the aortic arch with compression of trachea.

the aorta are not rare. As to whether the aneurysm is saccular or diffuse depends upon the extent of the underlying medial disease.

The course of development involves first a dilatation due to weakening of the media. In the diffuse form this does not lead to complete disappearance of the structures of the media. In the saccular form, however, as dilatation proceeds, both musculature and elastica are lost and the wall of the sac is then made up of cicatricial type of dense fibrous tissue. Although the sac is commonly lined by endothelium as the result of proliferation of the original lining cells, no other original structures of the aortic wall are to be found. Two im-

portant features of aneurysms deserve consideration, namely, *thrombus formation and erosion*. In the diffuse forms, thrombosis is absent or only local and caused by the roughening of the diseased walls, but in the saccular forms thrombosis is common. With the formation of the sac there are present a roughened wall and a somewhat slowed and disturbed circulation, so that a thin film of thrombus is deposited, whose surface conforms to the chord of the arc of the saccular dilatation. As the sac dilates in all directions, a larger arc with greater concavity is formed, leaving a space between the flatter thrombus and the dilating wall. Consequently another clot is deposited between the original thrombus and the wall of the aneurysm. This is repeated as dilatation progresses and finally results in the formation of a laminated clot whose youngest members are nearest the wall of the aneurysm. Since the wall itself is made up largely of cicatricial fibrous connective tissue, organization of the clot does not proceed very rapidly and the thrombus is almost never extensively adherent to the aneurysm wall. It probably serves a protective purpose because the more completely filled the sac is by the clot, the less is the distending pressure of the arterial blood against the wall. Thus, if the clot fills the aneurysm so that it presents a small surface at the neck of the aneurysm, there will be a pressure of so many millimeters of mercury against a limited surface, whereas if the entire wall of the aneurysm were exposed, the same distending force would be operative over a much larger surface. Thrombosis therefore tends to limit the growth of the aneurysm. The erosion of aneurysms is in large part an inflammatory process. The situation and direction of expansion of the aneurysm determines the structures which are eroded by its growth. The presence of this abnormal structure with the internal distending force results in a low grade, subacute or chronic inflammation in the immediate neighborhood with connective tissue growth which, as the aneurysm extends, comes to constitute a part of its wall. The inflammatory process is associated with destruction of the essential tissues of the neighboring structures, and these are indirectly replaced by the aneurysm itself. Thus, erosion, may occur into the trachea, into the esophagus, into the pleural cavities, through the anterior chest wall, and into the spinal column. In the latter situation, the bony structures, being more vascular, partake more readily in the reactive inflammation, and are thus eroded more successfully than the less vascular cartilage. Other situations of aneurysms of this type include particularly the popliteal, femoral, carotid, subclavian and innominate arteries.

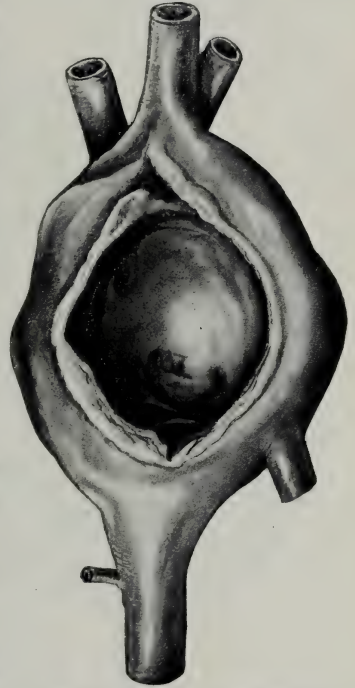


FIG. 219—Fusiform aneurysm of popliteal artery.

The clinical manifestations of aortic aneurysm depend to a considerable extent upon the situation, but pressure upon various surrounding structures may produce such symptoms as dyspnea and dysphagia. Similarly, local or general passive hyperemia may be induced by pressure upon veins. Inflammatory inclusion of the recurrent laryngeal nerves or stretching by the aneurysm may produce symptoms referable to the larynx. Adhesion to the trachea produces tracheal tug. The physical signs and x-ray findings are usually characteristic. The influence upon circulation depends fundamentally upon the introduction into the vascular tube of an expansile sac. This may damp the pulse wave so that it is slower in ascent and smaller than normal. The situation may be such as to produce inequality of the arterial pulses upon the two

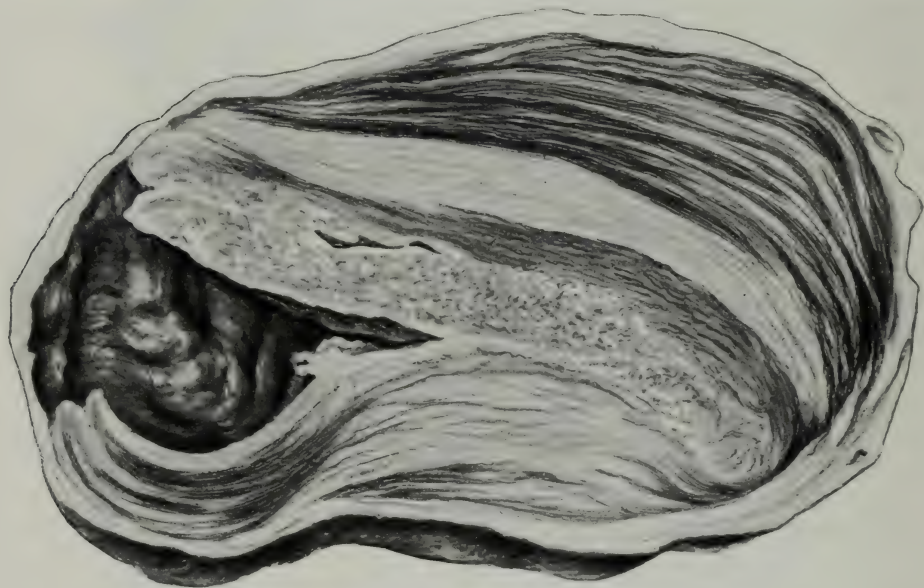


FIG. 220—Laminated clot in a saccular aneurysm of the aorta.

sides of the body. Aneurysm of itself does not produce any serious interference with circulation and does not lead to hypertrophy of the heart.

Hemorrhages from rupture of aneurysms may occur into viscera or body cavities. In the pleura or pericardium they may produce death by interference with function of the contained organs. In the peritoneum or pleura, death may result from loss of blood. Sometimes the hemorrhages may be in the form of slight leakage and infiltration of surrounding tissues and this often warns of larger hemorrhage. Erosion on skin surfaces or into surfaces communicating with the exterior such as trachea, esophagus and gut may be followed by fatal hemorrhage when rupture occurs. In these situations trauma, infection or digestion may aid in the rupture. Rupture to form arteriovenous communication is referred to in that connection.

True traumatic aneurysms result from traumatic influences which rupture either adventitia alone or adventitia and media, so weakening the wall that

distension occurs. Swallowing of bones and foreign bodies of various kinds, as well as stab wounds, fractures, bullet wounds and other similar accidents may produce the lesion. These are usually saccular in form and tend to early rupture.

Dissecting aneurysms are the result of rupture of intima and part or all of the media, due to internal distending force, operating upon thin or diseased arterial walls. These may occur in any part of the arterial system but are seen most frequently in the aorta. The blood leaks through the partially ruptured wall and dissects between the layers, usually in both directions from the point of rupture. In this way large amounts of blood may accumulate between the layers of the vessel wall. Surrounded by otherwise healthy tissue, organization is likely to proceed fairly rapidly. As a rule, the condition is fatal after a variable period of time. Rupture of the outer layers may lead to external hemorrhage. The affected vessel may show simple arteriosclerosis or may be thin as the result of congenital anomaly such as coarctation of the aorta or congenital hypoplasia. Krukenberg confirms the finding of Babes and Mironescu, that in some cases there is apparently a primary dissecting mesaortitis which prepares the way for dissecting aneurysms.

Embolic or mycotic aneurysms may be bland or infected.

The simple embolic aneurysms are due to lodging in small vessels of hard particles such as small pieces of calcified arteries or valves or calcified thrombi, which because of their density penetrate into the wall of the vessel and lead to local dilatation. Such a condition is reported more particularly in the vessels at the base of the brain. The infected embolic aneurysms are also often called mycotic aneurysms. These have been studied extensively, as indicated by the reports of Richey and Maclachlan, and of Stengel and Wolferth. They are likely to be multiple and occur in such infections as acute articular rheumatism, scarlet fever, septicemia, typhoid fever and pneumonia. In the majority of cases endocarditis is associated with these infections. Infected

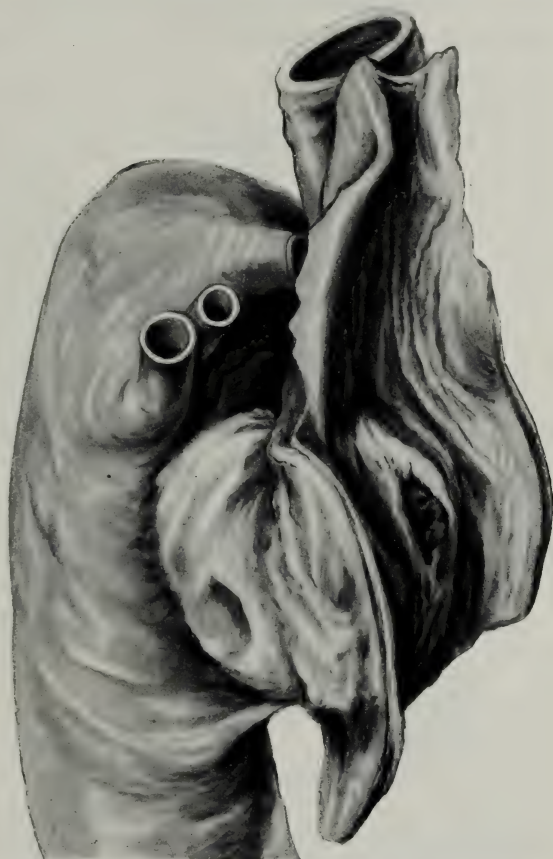


FIG. 221—Aneurysm of persistent ductus arteriosus with erosion into esophagus.

emboli may lodge in small vessels or upon the bifurcation of larger vessels and produce inflammation and weakening of vascular walls, so that local dilatation occurs. It is often difficult to distinguish between this condition and periarteritis nodosa, described above. Of similar nature are small aneurysms of the aorta due to infected emboli in the vasa vasorum, leading to acute suppuration of the media.

Erosive aneurysms are somewhat similar to the mycotic aneurysms. They are found in the sinuses of Valsalva and neighboring parts of the aorta, as the result of extension from acutely diseased heart valves, and development of

an ulcerative type of acute endarteritis with destruction of intima and underlying media.

False or Spurious Aneurysms.—A puncture wound of an artery as the result of shell, bullet or stab wounds, or erosion into the artery by some foreign body, may produce a localized hemorrhage or hematoma. The lesion of the vessel may close and the hematoma undergo organization and absorption. If, however, the wound of the vessel wall remain open, organization proceeds as usual, forming a sac around the hematoma. Communicating with the vessel, however, it is in the nature of an aneurysmal process and is usually referred to as a form of aneurysm.

Arteriovenous communications are usually of traumatic origin and due to simultaneous wounds of both vessels. It is possible, however, for an aneurysm of an artery to rupture into a vein and thus establish a communication, or very rarely for a local dilatation of a vein



FIG. 222—Saccular aneurysm of thoracic aorta eroding vertebræ. Note the resistance of the intervertebral discs.

to penetrate into an artery. An intermediate sac may also be formed through the production of a false aneurysm. If there be a sac between the artery and vein in the course of the communication, the condition is called *varicose aneurysm*. If there be no such intermediate sac, the condition is referred to as *aneurysmal varix*. Fairly large communications between reasonably large vessels may result in important alterations in the circulation, because both during systole and diastole there is a certain amount of direct shunting of blood from arterial to venous circulation. Since the flow exists at all times the pulse pressure is likely to remain normal, but both systolic and diastolic pressure are reduced (Hoover and Blankenhorn). Repair of the condition restores the normal dynamics of circulation. Hypertrophy of the heart may

occur in long standing cases, which Holman ascribes to increase of blood volume in the heart.

The term *miliary aneurysm* refers to small fusiform or saccular aneurysms of small arteries, particularly of the brain substance or more rarely of other situations such as the gut or lungs. The work of Ellis and of Pick shows that such aneurysms are extremely rare, if they occur at all. What appear to be aneurysms grossly are either minute dissecting aneurysms, between intima and media, or minute hematmata communicating with the ruptured sclerotic artery. Similar gross appearances may be produced by capillary hemorrhages into the perivascular spaces.

Tumors.—The angioma may be arterial in character and occurs in skin and in the cerebral or spinal meninges. It may resemble cirroid aneurysm. Of the



FIG. 223—Small aneurysms of the aorta due to healed acute endarteritis.

primarily malignant tumors, Benda states that primary sarcoma of the aortic wall has been reported. Malignant tumors may involve arteries from without, in the course of growth; the adventitia is infiltrated but the denser media often escapes. Tumor emboli may lodge in the pulmonary arteries, where they may or may not grow. In the former case a tumor thrombus forms, usually associated with blood thrombosis. The tumor may remain within the lumen or invade the wall to produce a larger metastatic mass.

Foreign Bodies and Parasites.—The foreign bodies are usually swallowed and may erode the aorta from the esophagus or as in one of our cases lodge in the stomach and erode the gastric arteries. Needles and fish bones are the commonest. In man the only parasites of importance which may invade arteries are the echinococcus cyst and the cysticercus racemosus.

Rupture of the arteries may occur as the result of the weakening influence of chronic disease, where internal pressure is raised beyond the resistance of the walls. The disease may be arteriosclerosis, syphilitic involvement, or erosion

by tuberculosis or other infection. Aneurysm formation does not necessarily precede rupture. Traumatic rupture may be by crushing wounds or direct cutting. Spontaneous rupture occurs in coarctation of the aorta and occasionally is seen in vessels which are otherwise apparently normal. Spontaneous rupture may be transverse, longitudinal, irregular or spiral, the last arrangement occurring more commonly in the arch of the aorta. Incomplete ruptures may produce dissecting aneurysm or rarely may heal.

VEINS

Retrogressive Changes.—The veins may show a variety of retrogressive changes, such as cloudy swelling and necrosis, when they are in the field of an inflammatory process. Aside from this, the simple degenerations are uncommon. Fatty degeneration may occur but is unusual. Amyloid is found much less frequently in small veins than in small arteries. Calcification is most likely to occur in connection with varicosities of veins but may also be observed as a part of metastatic calcification. Minute hemorrhages may be observed in the walls of large veins as a part of asphyxia or in such blood diseases as pernicious anemia and acute leucemia. Atrophy of veins occurs normally in the disappearance of such blood vessels as the umbilical vein. In this process, there is a proliferation of the connective tissue of the intima with occlusion of the lumen and subsequent conversion of the vein into a fibrous cord. Similar conversion of veins into fibrous cords may occur pathologically when veins are the seat of thrombosis. Although thrombosis of veins may occur as the result of trauma and interruption of continuity of the lining membrane, and may be produced experimentally by painting the outer wall of the vein with corrosives such as silver nitrate, nevertheless, in human medicine thrombosis is most commonly the result of inflammation either extending through the wall of the vein or originating within the vein.

Inflammation. Acute Phlebitis.—Acute inflammations of the smaller veins are a practically constant accompaniment of any localized inflammatory reaction. The numerous vascular phenomena of inflammation affect smaller veins and venules and from these vessels a considerable part of the exudate may originate. As the inflammation progresses the veins become thrombosed, which process serves as a protection against wide dissemination of the infecting organisms. It is only in unusual cases that such involvement of veins leads to a generalized infection of the body. Exception to this rule is found, however, in infections of the uterus where a suppurative endometritis is often accompanied by disease of the enlarged uterine veins, from which bacteria may gain entrance to the general blood circulation. Of great importance, however, is inflammation of the large and independent veins. Through trauma of the vein or by the retrograde passage of infected emboli, there may occur a primary acute endophlebitis which, since it is so commonly associated with thrombosis of the vein, is designated as a thrombo-endophlebitis. More common, however, is origin from without the vein, such as may be due to local extension of a suppurative process so as to include the outside of the vein, or

transmission to the vein wall through lymphatics. Thus, there is established an acute periphlebitis. Whether originating within or outside the vein, the process rapidly involves all the structures of the wall, and in the majority of instances it is impossible to distinguish an endo- or periphlebitis. The wall of the vein is infiltrated with this inflammatory exudate and as the endothelium becomes involved, thrombosis rapidly ensues. The thrombus furnishes an excellent field for growth of bacteria and extension of the inflammatory process. This may then continue along the course of the vein. Examples are seen in the case of suppurative mastoid disease with involvement of the jugular vein and the venous sinuses of the head. Similarly, acute suppurative appendicitis may produce an important thrombophlebitis of radicals of the portal vein. In certain instances where resistance is high, the thrombosis of the infected vein may serve to limit the progress of the infection, and subsequently undergoes organization. In other cases the extension of the inflammation into the thrombus converts this into a mass of pus, from which emboli may be transmitted to other parts of the body or from which bacteria may gain entrance to the blood stream. The results of embolism from the infected thrombi depend upon the situation of the primary disease. Thus, if the lesion be in the portal circulation, emboli become lodged in the smaller divisions of the portal vein in the liver and may produce multiple abscess of the liver. If the primary process be in the general circulation, other than the portal system, emboli may lodge in the pulmonary artery and produce abscesses of the lung. From the abscesses in the liver or in the lung, access may be had to the arterial circulation and a general pyemia develop. With either pyemia or septicemia, acute endocarditis may develop and serve as an additional focus for dissemination of bacteria.

Grossly, the vein the seat of an acute thrombophlebitis is usually somewhat distended and firm. When opened, the lumen is found to be filled with the thrombus which has undergone more or less complete suppuration. Upon removal of the somewhat adherent thrombus the lining wall is found to be rough and more or less necrotic. Microscopically, the entire vein wall is infiltrated with leucocytes and other cells of the acute inflammatory exudate, associated with edema and necrosis. The inflammatory exudate infiltrates not only the walls of the vein but also the thrombus contained within it.

Chronic phlebitis may or may not be associated with thrombosis. It may be secondary to such chronic infections as tuberculosis or syphilis, secondary to localized or general dilatations of the veins to be described subsequently, may be a part of thrombo-angiitis obliterans or may constitute a part of that rare disease sometimes spoken of as progressive thrombosis of the veins. In the last named condition trauma, or some unknown condition may establish thrombosis in any vein of the body. Subsequently, other veins become involved, usually not by direct extension, until a number of chronic thrombi may be established in various situations. Any variety of chronic thrombophlebitis shows fibrosis of the entire wall of the vein with atrophy of the muscle and with greater or less degree of organization of the thrombus. *Phlebosclerosis* differs from arteriosclerosis in that only rarely are there intimal plaques of thickening,

hyalinization and calcification formed. As a rule, the phlebosclerosis is a more diffuse process involving all the walls of the vein, associated with atrophy and sometimes disappearance of the musculature. In this diffuse lesion hyalin may occur, but subsequent degenerative processes such as are seen in arteriosclerosis are not likely to be found (Stahl and Zeh).

Granulomata. Tuberculosis.—In the involvement of veins by tuberculosis, it is often possible to distinguish sharply between a tuberculous periphlebitis and a tuberculous endophlebitis; the former is probably much more common. Thus, in the enlargement of a tuberculous focus the process may extend along the adventitia of veins, producing a chronic tuberculous periphlebitis. Sooner or later the involved vein becomes thrombosed and subsequently organized. Such structures are particularly in evidence in the trabeculae of tuberculous cavities of the lung. Tuberculous endophlebitis may be due to lodgment of tubercle bacilli within veins, or may be due to the extension of tuberculosis through the wall of the vein with involvement of the intima. In the former case, small, rather flat, discrete, subintimal tubercles are observed. In the latter, the tubercles are less numerous and project into the lumen of the vein after involvement of media and intima. Benda states that even although pulmonary tuberculosis is much more common in the upper lobe of the lung, tuberculous endophlebitis is more often observed in the lower lobe. This serves as a focus of dissemination of tubercle bacilli since thrombosis, although it occurs, is likely to be slow in development.

Syphilis.—Very commonly the veins in the neighborhood of primary or secondary lesions of syphilis show infiltration of lymphocytes and plasma cells either around the vein, in the adventitia or in the walls of the veins themselves. The same picture may be found in the organs of congenital syphilis (Ekehorn). This may be preceded by a chronic proliferation of connective tissue, rather moderate in degree. Sometimes the smaller veins in the neighborhood of the larger lesions, in addition to showing round cell infiltration, may also show thrombosis and subsequently obliteration. Occasionally, larger veins may show a nodular periphlebitis, with the microscopic picture of round cell infiltration and sometimes giant cell formation, due to syphilis, and there may also be a localized proliferation of the intima of large veins. Gumma may involve a large vein but practically never originates within the vein itself. There is nothing in the vein comparable to syphilitic mesarteritis.

Other Granulomata.—The leprous nodule may involve the wall of veins in its growth, producing a chronic inflammation and ultimately occlusion of the vein. Actinomycosis and glanders involve the veins in very much the same fashion as do acute suppurative processes.

Enlargement of Veins.—Enlargement of veins may occur because of hypertrophy of the vein or because of dilatation. Physiological hypertrophy occurs most particularly in the pregnant uterus. Pathological hypertrophy occurs when there is necessity for collateral circulation. Thus, when the portal circulation is interfered with by cirrhosis of the liver, drainage from the portal area is aided by collateral circulation through abdominal veins communicat-

ing directly with the inferior vena cava, through drainage into the azygos veins by way of the stomach and esophageal veins, and through the epigastric and internal mammary vein. The necessity for the flow of an increased mass of blood, leads to enlargement of these veins and an increase in the thickness of the wall due largely to growth of the musculature.

Dilatation of the veins may be either diffuse, under which circumstance it is commonly called phlebectasia, or circumscribed, when it is called varix. A cirroid form is also described but is difficult to differentiate from a combination of phlebectasia and varix. These dilatations may be the result of hypertrophy as indicated above and are very commonly the sequence of some condition which interferes with drainage of venous blood from a part. There are other instances in which dilatation of the vein appears to be due to some inherent weakness within the wall of the vein or to lack of support by surrounding structures. Thus, repeated pregnancies, or the thrombosis following typhoid fever, may lead to varicose veins of the leg; chronic constipation with pressure upon the hemorrhoidal veins by solid masses of feces leads to hemorrhoids. Cirrhosis of the liver may lead to anal hemorrhoids, to a dilatation of superficial veins around the umbilicus, often called the *caput Medusæ*, or to dilatation of veins at the lower end of the esophagus, sometimes referred to as esophageal hemorrhoids. It is often difficult to explain the dilatation of veins of the pampiniform plexus, more common in the male but often occurring in the female, referred to as varicocele, except by supposing inherent weakness of the veins. Simple phlebectasia may occur as cylindrical or fusiform dilatation of the veins. Commonly, however, this is associated with varicosities or localized dilatations which are the venous prototype of aneurysms. Thus, great tortuosity of the veins ensues and adjoining varicosities may communicate. The vein wall loses its elasticity and is sometimes thickened by fibrosis. The interior may show plaque-like thickening of the intima. Local or widespread thrombosis may follow. Microscopically, there is found fibrosis of all the walls of the vein with atrophy or even complete disappearance of musculature and with interruption or disappearance of elastica. There is often infiltration of lymphoid and plasma cells, more particularly in the adventitia. If thrombosis be present for sufficient length of time, organization will occur.

Dilatations of veins may give no symptoms whatever, or may be distinctly painful. The latter is commonly true of anal hemorrhoids where infection is common and subacute or acute inflammation is likely to occur. Repeated attacks of acute inflammation lead to chronic inflammation of these veins. Thrombosis, of course, is more common when infection or inflammation has occurred. In the veins of the leg, infection or further extension of the disease due to trauma is not uncommon, and the general disturbance of circulation of the extremities may in part account for the troublesome trophic ulcers of the leg. Rupture of the veins of anal hemorrhoids is not likely to be extensive and the consequent hemorrhages are usually small and frequently repeated. It is only rarely that severe hemorrhage occurs in this situation. In the esophageal veins, however, rupture may be fatal. Under favorable circumstances the

thrombi undergo organization, but may subsequently become calcified and if the vein is in a deep seated position, the phlebolith may produce confusing x-ray pictures.

Although insufficiency of the valves of the vein was formerly believed to be responsible for the dilatation, it is now known that the pressure in the peripheral veins is due principally to *vis a tergo*. Associated with poor drainage, this shows its effects in the dilated parts of the vein. Veins that are not well supported are more likely to show dilatation than those surrounded by viscera or muscle. It is at least possible that the rings around the valve may dilate more slowly than the rest of the vein and therefore produce a point of relative obstruction to circulation. The effect of damming back of blood varies with different individuals, in some producing varicosity and in others not. It is probable that low grade acute or chronic inflammations may account for the weakening of the vein wall and the consequent local or general dilatation. Yet it is also probable that in certain cases, inherent differences in resistance of the veins play an important part in determining the development of varicosity.

Tumors.—Aside from angiomas in which veins may play a part, other *primary* tumors are extremely rare but are said to include endothelioma, myoma, angio- and other forms of sarcoma.

Veins are of great importance in the dissemination of malignant tumors, which in their growth invade and grow through the walls of the veins. Tumor and blood thrombi are formed. The tumor may extend by growth along the veins, or tumor fragments are dislodged to constitute emboli, thus providing for hematogenous metastasis. Because of their richer vascularization, sarcomata metastasize in this way more frequently than carcinomata. Benda believes that the invasion of vascular walls by leucemic nodules introduces into the blood stream additional lymphocytes or even the cells of the myeloma.

Parasites.—The most important are the three species of schistosoma, namely *S. hematobium*, *S. mansoni* and *S. japonicum*, which are found in perivesical and perirectal veins and arteries. The vessels usually show no lesion but in occasional instances may show marked intimal proliferation. Echinococcus cysts of the liver may break into hepatic veins and lead to new cysts in heart or lungs. Foreign bodies may erode into veins as into arteries.

LYMPHATIC VESSELS

Inflammations. Acute Lymphangitis.—Acute lymphangitis is very common and may be caused by bacterial infection from wounds of various kinds. It may also arise as a primary lesion, may be associated with such infections as syphilis and gonorrhea, and may follow the skin reactions to poisonous plants or the bites and stings of insects. Warthin recognizes three types namely, the simple, purulent, and proliferative. Simple lymphangitis is more truly a perilymphangitis. Thus, there is edema and cellular infiltration in the outer wall of the lymphatic with, as a rule, only cloudy swelling of the lining endothelium. The lymph within the vessel may remain fluid, or coagulate so as to constitute a

thrombolymphangitis. A complete restoration to normal may follow the subsidence of the inflammation. At its height, the lymphangitis causes the red line commonly seen extending up extremities as the result of infected wounds or other lesions. The line is somewhat tortuous and usually terminates at a regional lymph node. The surgeon sometimes differentiates between a reticular lymphangitis in which there is localized swelling and redness, and a "tubular" lymphangitis as described above. The purulent form shows infiltration of leucocytes through the wall of the lymphatic, and swelling and desquamation of the endothelium. The lumen of the vessel is likely to be filled with pus which may be coagulated to form a purulent thrombolymphangitis. In those vessels provided with valves, the swelling between the valves may give the lymphatic a beaded appearance. Abscesses may form at any point in the course of the lymphatic but are particularly likely to develop in the lymph nodes into which the vessels drain. Acute proliferative lymphangitis may be seen in connection with gonorrhea or in the acute stages of syphilis. The wall of the vessel is considerably thickened by the formation of fibroblasts, sometimes associated also with proliferation of the lining endothelium. There is likely to be edema and a slight degree of cellular exudate in the outer wall of the lymphatic and in the surrounding structures.

Chronic Lymphangitis.—This may be due to chronic infections, to prolonged absorption through the lymphatics of toxic material, to invasion by malignant tumors and to the presence in the lymphatics of parasites such as the filariæ. The walls are thickened and the vessels become much more prominent than normal because of the fibrous overgrowth, and the process may become so advanced as to obliterate the vessel completely. In the earlier stages, the swollen endothelial cells may be very prominent in histologic sections and may be mistaken for invading tumor cells. The condition is common in serous surfaces, particularly the visceral pleura where the anatomical lobules may be sharply marked out by the gray, opaque lines of lymphatic vessels. This is especially common in various forms of pneumokoniosis and in chronic tuberculosis. If the network of the lymphatics be sufficiently intricate, no serious results are observed but if the process involve a large draining lymphatic or a plexus of lymphatics, lymph may be dammed back into the tributary vessels with the production of edema.

Tuberculosis.—As pointed out in the section on granulomata, lymphatic vessels offer a favorable situation for the growth of tubercles. Tuberculous involvement is therefore extremely common. It may occur as miliary tubercles within the wall of the lymphatic or the tuberculous process may occupy both lumen and wall, converting the lymphatic into a more or less caseous nodular mass. The latter process is seen particularly well in perivascular and peribronchial tuberculosis of the lungs. The former variety, in which discrete miliary tubercles are easily apparent, is especially well seen in tuberculous involvement of the lymphatics of the intestine and mesentery.

Syphilis.—In the neighborhood of the chancre an acute proliferative type of lymphangitis is likely to be observed, and the same may be true in the

neighborhood of secondary lesions. In late syphilis a general fibrosis of many lymphatics may be observed. These acute and chronic forms of lymphangitis associated with syphilis are not characteristic of that disease in gross or microscopic appearance. Only rarely are gummata found in the walls of larger lymphatics.

Dilatation of Lymphatics.—Owing to the extreme complexity of communication between smaller lymphatics, obstruction must be very extensive in these areas, or must operate upon a large vessel, in order to produce a damming back of lymph and dilatation of the vessels. Such obstruction may be due to disease of the lymphatic itself such as a chronic obliterative lymphangitis, occlusion by tumor growth, pressure from without by tumors or cicatricial tissue, enlarged lymph nodes, etc. or may be due to presence within the lymphatic of parasites, the most striking example being the *filaria sanguinis hominis*. The dilatation may be diffuse or is sometimes localized with aneurysm-like sacs and sometimes produces fairly large lymph cysts. In peripheral parts, obstruction to the main lymphatic drainage is likely to give rise to marked cutaneous and subcutaneous edema of chronic type. This constitutes elephantiasis, observed particularly in the lower extremities and scrotum. With the chronic edema there is likely to be overgrowth of connective tissue, not only in the lymphatics but in the surrounding tissue; and not infrequently the skin itself is considerably thickened by the fibrous overgrowth. The congenital forms of elephantiasis are of the nature of tumor-like anomalous growth of the lymphatics; the acquired form as observed in non-tropical latitudes may be due to any of the causes given above. In the tropics the most frequent cause is filariasis. If the dilated vessels rupture, the condition known as lymphorrhagia ensues. Lymph may leak into peritoneum, pleura, pericardium, bladder, kidney and other structures. If the lymph be rich in fat, the fluid assumes chylous characters.

Tumors.—The so-called benign tumor of greatest importance is the lymphangioma which occurs most commonly as a congenital condition. As has been mentioned in the chapter on tumors, it is difficult to say whether these tumors are to be regarded as true neoplasms or simply as anomalies of development. In those forms which occur later in life it is equally difficult to distinguish true lymphatic neoplasm, and dilatation and hyperplasia in preëxisting lymphatics. The congenital forms are more likely to be of cystic character, as well exemplified in macrocheilia, macroglossia and the congenital cystic tumor of the neck, the so-called hygroma colli cysticum. Those tumors appearing as moles, warts and nevi are less likely to be cystic in character. It is probable that endothelioma may originate from the endothelium of lymphatic vessels, and sometimes there is observed a combination of endothelial growth and lymphatic proliferation referred to as the lymphangio-endothelioma. As is well known, the lymphatic vessel serves as a mode of transmission of malignant tumors, more particularly the carcinoma. The growth of carcinoma through lymphatic vessels is commonly observed and may or may not be associated with a chronic lymphangitis. The question as to whether or not transmission

may occur by embolism of small tumor masses or cells through the lymphatics has been discussed in the chapter on tumors.

Thoracic Duct.—This largest lymphatic of the body may be anomalous, as exemplified by the presence of two ducts, or may be represented by a lymphatic plexus. Anomalies of termination are fairly frequent so that the outlet may be double or may enter into almost any of the large veins of the upper thorax and the neck. It is supposed by some that the fat of fat embolism may gain access to the circulation through the lymphatic ducts; whether or not this be true, it is certainly possible that the amount of fat draining into the blood through the thoracic duct may seriously augment that which gains entrance to



FIG. 224—Drawing of tuberculosis of retroperitoneal lymph nodes and of the thoracic duct.

the circulation directly. The thoracic duct is subject to the same type of acute and chronic inflammations as described above for the other lymphatics. It is commonly the seat of tuberculosis and probably serves in a large percentage of cases for the entrance of tubercle bacilli into the blood stream, thus constituting a common cause of disseminated miliary tuberculosis. Syphilitic gumma of the thoracic duct is occasionally observed, and Warthin states that in congenital syphilis there is usually a large number of spirochetes in the walls of the duct. Dilatation of the thoracic duct may occur as the result of pressure from thoracic tumors or aneurysms of the aorta, or from lesions within the duct such as thrombosis, tuberculosis and tumor involvement. The dilatation of the duct itself is not easily recognizable, but the receptaculum chyli may be so distended as to constitute a mass palpable through the abdominal wall. Associated symptoms of importance are chylous ascites, chylous hydrothorax and hydropericardium, and chyluria.

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CHAPTER XIV

THE HEMATOPOIETIC SYSTEM

ANEMIAS.

POLYCYTHEMIAS.

LEUCEMIAS.

SPLEEN.

LYMPH NODES.

BONE MARROW.

RETICULO-ENDOTHELIAL SYSTEM.

Introduction.—The hematopoietic, hemopoietic, or as Krumbhaar prefers, the hemolytopoietic system, of adult life comprises the spleen, lymph nodes, bone marrow, the reticulo-endothelial apparatus, and the liver. The liver is considered in a special chapter. The thymus gland is discussed in the chapter on ductless glands. Brief consideration will be given the anemias, polycythemias and leucemias; for a more complete description the reader is referred to texts on hematology. The anemias are classified as primary and secondary, and in addition a few special forms deserve mention.

Secondary Anemias.—This term refers to those conditions characterized by reduction in the number of circulating red blood cells, produced by a variety of fairly definite causes. Included in this list are hemorrhage, either multiple small hemorrhages or a single large hemorrhage; the hemorrhagic diseases such as purpura; acute infectious diseases; chronic infectious diseases, particularly tuberculosis and syphilis; other chronic diseases such as chronic nephritis; malignant tumors which operate either by the production of hemorrhage, by erosion, by invasion of the bone marrow or perhaps by cachexia; acute poisoning such as that by carbon monoxide; chronic poisoning such as by lead; animal parasites such as the *dibothryophyllum latum* and *ankylostoma duodenale* or *necator Americana* and *balantidium coli* (Logan); and parasites of the blood itself, especially the *plasmodium malariae*. The causes may then be loss of blood, destruction of circulating erythrocytes and depression of bone marrow activity. Except in the case of hemorrhage, it is difficult to say that any one factor is responsible for the anemia. Thus, malignant tumors may destroy much of the bone marrow with an accompanying anemia, but it is impossible to exclude the operation also of some poisonous cachectic substance directly upon the red blood cells or their precursors. Conversely, the malarial parasite destroys erythrocytes, but it is also possible that there may be some toxic depression of bone marrow. Brown and Roth believe that the anemia of chronic nephritis is due principally to depression of the bone marrow. Tumors of the pyloric end of the stomach or of the pancreas may show considerable general anemia, but the carefully controlled studies by Ash show that uncomplicated inanition does not produce serious changes in the blood, and it is probable that the effects on the blood of tumors of the alimentary canal are not due solely to starvation. Muscular exercise increases

blood destruction but is of little importance as a cause of anemia (Rous). The anemias, therefore, require careful investigation as to causes and their possible poisonous products, blood changes, lesions of bone marrow, and other parts of the hematopoietic system and the metabolism of hemoglobin and of the body in general.

The blood picture of secondary anemias varies somewhat with the nature and severity of the cause. The number of circulating erythrocytes is definitely reduced. There is, however, difference of opinion as to whether the blood volume is normal, reduced or increased. It seems likely, however, that the mechanism in the body for maintaining a fairly constant blood volume is such that there is no lasting change. The hemoglobin content is usually reduced in direct proportion to the reduction of red cells, or somewhat more, but variations are likely to occur, especially in the case of *dibothrophyllum latum* anemia in which the cells are reduced in greater degree than the hemoglobin. According to the work of Capps and of Haden, the size and volume of the red cells of prolonged secondary anemia are reduced. Examination of stained smears of the blood in an early or moderate case of secondary anemia shows no notable changes in the red cells. In the more prolonged and more severe forms there may be definite central pallor of the cells, anisocytosis and poikilocytosis. Nucleated forms may also be observed, and in the *dibothrophyllum latum* anemia there may be preponderance of megaloblasts over normoblasts. Polychromatophilia may be observed and in that form of secondary anemia due to lead poisoning, basic stippling of the red cells is almost constant. In the acute anemia following large hemorrhage, Drinker points out that the number of leucocytes rapidly rises, reaching its height in a few hours after the hemorrhage. Lee and Minot state that in chronic anemias there is less tendency to leucocytosis. Anemias of acute infections are accompanied by the leucocytosis incident to the cause. Ecker and Rees find, following a large hemorrhage, a rapid increase in the number of platelets in the circulating blood.

Primary Anemias.—These anemias, of unknown cause, include chlorosis and *primary progressive pernicious anemia*, also called pernicious anemia, Addison's anemia and Biermer-Erlich anemia. A disease practically identical with pernicious anemia occurs in the puerperium or in pregnancy (Rowland) and in the course of syphilis (Cummer). Cabot found pernicious anemia commonest in the fifth decade of life, unusual before the thirty-fifth year, and about twice as frequent in males as in females. Meulengracht suggests a hereditary constitutional predisposition. The disease has been ascribed to many causes but these have not been finally established. Two suggestions deserve consideration. Achlorhydria has been found to precede many cases and in one by as much as fourteen years (Sturtevant), but it is at least possible that both the anemia and the achlorhydria are due to the same fundamental cause. Kahn and Torrey have found unusually large numbers of *bacillus welchii* (*aërogenes capsulatus*) in the stools of patients with pernicious anemia, and have demonstrated a soluble product which produces a similar disease in monkeys. Other bacteria, as for example, a hemolytic proteus bacillus isolated by Kline from bone mar-

row, have essentially the same property. Whilst bacteria may play a part in the cause, it is not possible to say that any particular organism is specific.

Pernicious anemia produces slight if any wasting of the body. The skin and body fat often have a lemon yellow tint, probably due to the presence of bile pigment in the plasma, as indicated by Blankenhorn. Particular importance is given by Hoover to manifestations due to lesions of the spinal cord, more particularly acro-ataxia and acroparesthesia. The number of circulating red blood corpuscles is usually markedly decreased but their volume is usually about normal or increased. The hemoglobin is not reduced in proportion to the reduction of number of cells and therefore the color index is usually one or more. As noted above, the plasma frequently shows the presence of bile pigment. Examination of stained films shows considerable anisocytosis (lack of uniformity in size of erythrocytes) with predominance of macrocytes (large erythrocytes). Polychromatophilia and even basic stippling are not uncommon. Nucleated forms are practically constant, and although in many cases the total number of megaloblasts (large erythroblasts) does not exceed that of normoblasts, nevertheless the appearance of a considerable number of megaloblasts is of significance. Reticulated erythrocytes are increased in number. The resistance to hypotonic salt solutions is usually increased but may be reduced (Pearce, Krumbhaar and Frazier). The number of leucocytes is usually somewhat decreased and in the differential count the decrease is seen to affect particularly polymorphonuclear forms, with a relative increase of lymphocytes. Myelocytes occur but not in any great numbers. The blood platelets are usually reduced in number but this is by no means constant, and prothrombin is likely to be reduced (Drinker and Hurwitz). This probably accounts for the hemorrhagic tendency and the prolonged bleeding time of pernicious anemia.

Aplastic anemia is related by some authors to pernicious anemia, and regarded as a stage in which the bone marrow is exhausted, but it seems more probable that it is an independent affection or one associated with such diseases as purpura. This disease occurs in earlier life than pernicious anemia, is more common in women, and runs an extremely acute course. The anemia is severe and commonly complicated by hemorrhage. The blood examination shows a lower color index than pernicious anemia, absence of nucleated red cells and among the white cells a very marked relative increase of the lymphocytes. Furthermore, the red cells do not show such severe grades of anisocytosis and poikilocytosis and the platelets and prothrombin are decreased. Benzol may, by depression of bone marrow, produce anemia of aplastic type.

Chlorosis.—This is the so-called green sickness of young girls, occurring especially between the ages of fifteen and twenty-five years. At this period of life it is at least possible that the onset of menstruation may have some bearing upon the disease, but nothing has been proven in this connection. Cabot is particularly impressed with the fact that the disease is common among girls in household service and may therefore have some relation to general hygienic surroundings and modes of life. The symptoms are usually mild, and associated with slight increase of total acidity of the gastric contents, there is a

morbid appetite directed particularly toward ingestion of alkalis. The blood examination shows a slight or moderate reduction in the number of erythrocytes with a very considerable or even marked reduction of hemoglobin, thus producing a low color index. It is generally accepted that there is increased volume of the blood due to serous plethora. The stained film shows cells whose average size is likely to be smaller than normal, and central pallor may be very noticeable. Anisocytosis, poikilocytosis and nucleated forms are not commonly observed. Occasional nucleated forms are practically always normoblasts. The leucocytes may show slight variation in total and relative numbers but these changes are never marked (see Campbell).

Sickle Cell Anemia.—According to Sydenstricker, "sickle cell anemia is a familial and hereditary disease showing no sex preferences and probably confined to the negro race." It is apparently a defect in the erythrocytes, or the hematopoietic system, which favors the development of anemia of secondary type, hemolytic in nature and characterized by the fact that the principal manifestation of poikilocytosis is in the form of crescent shaped and stellate erythrocytes.

Pathological Anatomy of Anemias.—Of the types of anemia described above the one which shows the most severe changes throughout the body is pernicious anemia, but somewhat similar changes may be observed in the other forms. For this reason, the entire group is included in the presentation of the pathological anatomy. In the postmortem examination of a case of pernicious anemia the state of nutrition and color of the muscle may be excellent as compared with the extreme pallor of the body. The skin and body fat are likely to show a typical lemon yellow tint. The blood is thin and watery, but except for their small size the clots are not different from those of normal blood. Petechiæ may be found in various parts of the body. The heart both grossly and microscopically may show either hypertrophy or atrophy, and microscopically areas of both. The striking change is fatty degeneration, easily visible through the endocardium as yellow tigering. Cloudy swelling and fatty degeneration may in fact be common to all the parenchymatous viscera. Similar changes may be observed in occasional cases of severe and prolonged secondary anemia. In the liver, cloudy swelling and fatty degeneration are common, but the most significant change is hemosiderin pigmentation, visible both grossly and microscopically and in both instances demonstrable by the potassium ferrocyanide and hydrochloric acid test. Microscopically, the pigment is found to be present in the form of minute granules within the liver cells throughout the lobules, and careful examination may show similar granules within some of the endothelial cells lining the sinusoids. It is rare for any secondary anemia to show such extensive pigmentation. In severe and prolonged anemias the liver may regain to a limited extent its function as an erythroblastic organ, and foci of marrow-like cells are found. The kidneys may show cloudy swelling and fatty degeneration and sometimes hemosiderin pigmentation of the tubular epithelium. The spleen of pernicious anemia is usually of about normal size but may be larger or smaller. Pigmentation may

be demonstrable but is much more a feature of secondary than of primary anemia (McMaster et al.). Microscopically the arterioles, sinusoids and follicles appear normal, but the pulp contains a larger number of red cells than is usual. Small granules of hemosiderin may be found within phagocytic endothelial cells and not infrequently in extracellular position. In addition, phagocytes may be encountered containing whole red blood corpuscles or their fragments. In secondary anemias the phagocytosis of red blood corpuscles may be more prominent but pigmentation is not likely to be so severe. If the cause of the secondary anemia be an infectious disease or the case constitute one of the forms of splenic anemia, the spleen may show an acute or chronic hyperplasia. Occasionally, in pernicious anemia the microscopic examination of the spleen may reveal small islands of myelocytes and also of nucleated red cells. The lymph nodes show no characteristic changes, but the hemal lymph nodes may show definite hyperplasia and also considerable phagocytosis of red blood corpuscles and of pigment. The bone marrow of pernicious anemia is best studied in the long bones where there is found a hyperplasia or hypertrophy of the red marrow, which extends from the ends of the bone throughout the length of the shaft. This may even occur to a limited degree in secondary anemia, but it is rare to find the marrow of the shaft entirely converted into red marrow in conditions other than pernicious anemia. Microscopically, the amount of fat in the bone marrow is very much reduced or absent. In its place there is a cellular mass comprised of foci of cells of different types. Although the marrow grossly is red, nevertheless the microscopic picture shows hyperplasia of the white cell forming elements, including the myeloblasts and the myelocytes. There are also likely to be hyperplastic foci of lymphoid cells. Erythroblasts appear in large numbers and the majority of these are megaloblasts. Hemosiderosis and even phagocytosis of red cells may also be observed. In aplastic anemia the marrow is fatty or the seat of mucoid degeneration.

The alimentary canal may show hemorrhages in the mouth or other parts. Glossitis is fairly common. The stomach is likely to be the seat of a chronic atrophic gastritis, with thinning of the mucous coat and atrophy of the glandular substance. The spinal cord may show multiple small hemorrhages. Of greater significance is combined degeneration of, or occasional large hemorrhages of, lateral and posterior tracts, discussed in the chapter on nervous diseases.

Functional Disturbances.—Chemical and other studies of the secondary anemias have been confined particularly to those due to hemorrhage; pernicious anemia and chlorosis have also been well studied. The chemistry of these conditions is admirably discussed by Wells, and certain of the features have been referred to in our chapter on general pathology of circulation. Following a large hemorrhage there is almost immediate replacement of the fluid content of the blood so as to restore blood pressure, but this does not reach its height until about the third day. Consequently, there is a decrease in protein and an increase in salts and water, associated with a fall in total alkalinity. There is a depression of freezing point and of viscosity. Corpuscles may increase in size and specific gravity. There is an increase in nitrogenous meta-

bolism associated with an increased destruction of protein. Regeneration of red blood corpuscles proceeds rapidly, but as emphasized by Whipple, is influenced by the quality and quantity of the diet. The same increase in nitrogenous metabolism is often observed in pernicious anemia and in some cases there is an increased output of purins indicating a destruction of nuclei. In this condition, however, although there is a decrease in blood protein generally, that contained within the individual corpuscles is likely to be increased owing to the increase in size. Much interest is attached to the lipoids in pernicious anemia, for it has been thought that there is an increase in unsaturated fatty acids with a decrease in cholesterol which would give a chemical basis for increased destruction of red blood corpuscles. The investigations of Bloor and MacPherson, however, have shown that there is no regular increase in unsaturated fatty acids, although when the blood is reduced to more than half the normal value of red blood cells the total fat may be increased. While there may be low cholesterol and low lecithin in the plasma, the lipid composition of the corpuscles was found to be normal in most cases. "There was, therefore, nothing in their composition to indicate abnormal susceptibility to hemolysis." There is still the possibility that the blood fluids have some influence, and Clark and Evans have shown a definite decrease in the power of serum from patients with pernicious anemia to protect guinea pig erythrocytes against the hemolytic activity of sodium oleate.

The hemoglobin metabolism has been extensively studied, but lacking a thoroughly satisfactory knowledge of normal metabolism of this pigment and of iron, it is difficult to draw definite conclusions. As pointed out above there is an increased amount of blood pigment in the body, more particularly, however, in the liver. This has been taken to indicate that there is a great destruction of the blood in the portal circulation but is not supported by the experiments of McMaster and his colleagues. In the circulating blood the amount of iron is in excess of that found in the hemoglobin of the corpuscles. There is likely to be an increased production of bile which may not appear in the urine because, as Blankenhorn suggests, of some hypothetical combination with body protein. There is an increased output of stercobilin which, as Whipple points out, is far in excess of that to be accounted for by destruction of circulating erythrocytes. Warthin is of the opinion that blood destruction in anemia follows the usual mechanism but is simply considerably increased in amount. Peabody and Broun draw attention to the activity of phagocytosis of erythrocytes by cells of the reticulo-endothelial system, especially in the bone marrow. Whipple does not controvert the hemolytic character of pernicious anemia, but from his analysis of the available data, quite logically believes that there is an overproduction of pigment which may possibly be due to stimulation of bone marrow by the presence of hemoglobin.

In both secondary and primary anemias the capacity of the hemoglobin for carrying oxygen and carbon dioxide is not materially altered, but the quantity of these gases conveyed must be reduced in proportion to the absolute content of hemoglobin. Thus, as is pointed out by Lundsgaard and Van Slyke, cyanosis

is not observed in severe anemias. There is, however, very little tendency for anemias to show the symptoms of anoxemia. This is believed by Fahr and Ronzone to be due to a compensatory mechanism which includes increased systolic output and minute volume of the blood, with increased blood velocity due to lowered viscosity and "increased effective cross section of the vascular tubing."

Myelophthisic Anemia.—This is due to destruction of, or crowding out of, bone marrow by various lesions. Thus, the anemia of leucemias is probably the result of diminution of erythroblastic tissue due to hyperplasia of myeloblastic type of marrow. Malignant tumors, such as myeloma, and metastases, such as those especially from prostate or breast, may invade bone marrow so extensively as to reduce its function. Osteosclerosis with thickening of the bone and reduction of marrow may be of inflammatory origin or follow primary tumors (myeloma) or secondary tumors. If sufficiently extensive, osteosclerotic anemia (Assmann) may appear, with reduction of the number of erythrocytes and hemoglobin. The leucocytes may be reduced or slightly increased, but usually there is a relative lymphocytosis due to the reduction of myeloblastic activity of the marrow. Blood forming centers may occur in liver, spleen and lymph nodes (see Osterlin).

Anemias of Childhood.—Anemias in infancy and early childhood are likely to show confusing pictures, apparently in part because of the normal persistence of red marrow in the long bones. Thus, the anemias of all forms are likely to show a high color index and many nucleated erythrocytes, many of which are megaloblasts. The leucocytes are increased in number, often very considerably, with a high proportion of myelocytes and irritation forms. The spleen and often the lymph nodes are enlarged as the result of a chronic hyperplasia and, with the high leucocyte count, certain cases have been called pseudoleucemia infantum (von Jaksch). Such terminology is not justified, as the condition is essentially the same as other infantile anemias. The bone marrow is red, as usual in infancy, but according to Schridde shows microscopically many mitoses of the erythroblastic cells and is evidently in a state of great activity.

Purpura.—Although, as Minot points out, confusing border line cases sometimes occur, purpura and aplastic anemia are clinically different conditions. Pratt defines purpura as a condition in which spontaneous hemorrhages develop in and beneath the skin and mucous membranes. Changes in the blood and vascular walls are probably primary causes of the disease and hence the associated anemia is secondary. In many cases purpura is symptomatic and associated with acute infectious diseases producing hemorrhagic or "black" types of such diseases as smallpox, scarlatina, measles, diphtheria, etc. Purpura may be caused by chronic diseases such as nephritis, malignant tumors, tuberculosis, leucemias and primary anemias. Various drugs such as iodine, mercury, antipyrin, chloral, etc., may produce toxic purpura. Mechanical purpura may appear in prolonged passive hyperemia or in epileptic convulsions, whooping cough and asphyxia. Constriction of a part may produce capillary

hemorrhage, more especially where there is increased permeability of the walls as in scarlatina and scurvy (Rumpel-Leede phenomenon—Leede). Purpura has a seasonal variation, being more frequent in autumn and winter and occasionally seems to be hereditary. Aside from the secondary anemia due to hemorrhage, purpura simplex has no characteristic blood picture. In purpura hemorrhagica there is in addition to skin lesions, hemorrhage into the mucous membranes such as those of nose, alimentary canal, genito-urinary canal and other sites. Fever is common and if the patient be afebrile, the disease is often called purpura hemorrhagica of Werlhof. In purpura hemorrhagica there is usually severe secondary anemia and a marked reduction in the number of platelets. The bone marrow is depressed as regards platelets but not as regards erythrocytes or leucocytes (left-handed shift, Arnehl). Howell found normal content of prothrombin and antithrombin. The coagulation time and bleeding time are usually normal, but the clot shows reduced tendency to contract. The association of purpura and acute articular rheumatism is sometimes called Schönlein's purpura. Henoch's purpura or purpura abdominalis shows recurring attacks of purpura and crises of abdominal pain, often with vomiting and diarrhea. The pathological anatomy of purpura shows nothing of significance except the hemorrhages which may be found in any position in the body. Chronic purpura may be intermittent or more rarely continuous.

Hemophilia.—Pratt defines this as “an hereditary constitutional anomaly limited to the male but transmitted by the female, characterized by a tendency to bleed from trivial cuts and bruises, and by a marked delay in the coagulation of the blood.” The remarkable transmission through females to males has been studied in numerous instances, running through many generations without a well authenticated case in a female (Bullock and Fildes). The blood is not deficient in platelets, and spontaneous hemorrhages do not occur. The principal and most constant feature of the disease is delayed coagulation time of the blood, but the clot when formed is normally firm. Howell finds a reduction in activity or quantity of prothrombin, with a relative increase in activity of antithrombin. The hemorrhages may produce severe or even fatal secondary anemia.

Hemolytic Jaundice.—Hemolysis within the body may cause jaundice but the term hemolytic jaundice when referred to human disease is usually restricted, as Tileston points out, “to a form of jaundice usually chronic, in which diminished resistance of red cells to hypotonic salt solutions is a conspicuous feature, while bile pigment is present in the stools and absent from the urine. Enlargement of the spleen and anemia complete the picture.” Of the two forms of the disease, the congenital (Minkowski-Chauffard) is more common than the acquired (Hayem-Widal) type. The congenital form may attack a single individual in early life or members of three or four generations, affecting both sexes about equally and transmitted through either sex. Syphilis and tuberculosis may be associated but in no established causative relationship. The anemia is of secondary type but the hemoglobin may be relatively high. Reticulated erythrocytes are present in considerable number,

but the resistance of erythrocytes to hypotonic salt solutions is diminished. The leucocytes are usually normal. Fats and lipoids of the blood show no constant variations. Cholelithiasis is a common complication.

The acquired form may be cryptogenetic, without known cause, or may be secondary to such diseases as syphilis, malaria, tuberculosis, streptococcus septicemia and other acute infections, pregnancy, hepatic cirrhosis, carcinoma and leucemia. The anemia is severe, the resistance of erythrocytes less markedly diminished, and the jaundice slight or sometimes absent. In certain cases autohemolysins have been demonstrated.

The spleen is usually much enlarged, red, firm, and with chronic capsulitis. Microscopically, there is marked hyperemia, with pigment and even phagocytosis of red cells by endothelial cells in the sinuses, the connective tissue not being increased. The liver cord cells, the sinus endothelium of lymph nodes, the renal convoluted tubular cells, show hemosiderosis and the bone marrow is likely to show considerable hyperplasia, of erythroblastic and myeloblastic character.

In connection with the above, spirochetosis icterohemorrhagica, *spirochetel jaundice* or Weil's disease, deserves mention. The disease is caused by the spirocheta or leptospira icterohemorrhagica (Inada, Noguchi). There is secondary anemia, with or without leucocytosis, and jaundice. The pathological lesions include hemorrhages in various organs of the body, principally in the lungs; the viscera are likely to be icteric. Necrosis is found in the liver (Basile) and in the convoluted tubules of the kidney (McNee). The spleen is not enlarged but histologically shows phagocytosis of erythrocytes by endothelial cells, and sometimes large or small hemorrhages.

Polycythemia.—An increase in the number of circulating erythrocytes, a symptomatic polycythemia, may result from reduced partial pressures of oxygen as at high altitudes, congenital heart disease, passive hyperemia, dyspnea, blood poisons such as carbon monoxide and certain diseases such as syphilis and tuberculosis. Acute polycythemia may be produced experimentally (Lamson), but this has as yet no direct bearing on the human process.

Of importance is that chronic disease or syndrome called Osler-Vaquez disease, polycythemia rubra vera or megalosplenica, and erythremia. Weber, in accord with the opinion of others, regards erythremia as a primary "excessive erythroblastic activity of the bone marrow" associated with marked and persistent increase in the number of circulating erythrocytes. This view is shared by Minot and Buckman, who regard the erythroblastic activity as in some respects comparable to the myeloblastic activity of myeloid leucemia. The spleen is usually enlarged. The patient either has a dark, flushed appearance due to the excess of blood, the erythrosis of Lundsgaard, or is truly cyanotic. Various other signs and symptoms occur. The number of circulating erythrocytes is considerably increased and may reach twice the normal or more. The staining reaction and morphology are usually normal, but normoblasts may be found. The content of hemoglobin and the color index are high. The resistance of erythrocytes is increased. White cells are increased in num-

ber, especially the polymorphonuclears, and myelocytes sometimes appear. Platelets also are increased in number. All these facts indicate the great activity of the bone marrow. The blood volume and viscosity are increased (see Brown and Griffin). At autopsy all the organs show the plethora. The enlarged spleen shows little or no evidence of hemolytotoxic activity; thus, since the spleen as shown by Barcroft and coworkers accommodates itself to changes in blood volume, this enlargement is probably due principally to the increase in bulk of blood. Microscopically, there is an inconstant preponderance of erythroblastic over myeloblastic areas, but not as great activity as in pernicious anemia.

Of the cases which are secondary to other conditions, those due to cardiopulmonary disease are of importance. In these the polycythemia is probably secondary to deficient interchange of gases in the lungs and cyanosis is practically constant. Included here are the "cardiacos negros" cases of Ayerza. Congenital heart disease, chronic diseases of the lungs and disease of pulmonary artery may be found (Morse). In Warthin's case the underlying condition was syphilitic disease of the pulmonary artery. Erythroblastic activity of bone marrow is not likely to be prominent and the spleen enlargement, when it occurs, shows only hyperemia.

Leucemia.—The term leucocytosis refers to a temporary increase in the number of circulating white blood cells, without necessarily implying anything more than a compensatory reaction of the hematopoietic system. The causes and nature of this process have been discussed in the chapter on infectious diseases. The term leucemia, or leucocythemia, is more inclusive and covers not only the blood picture but numerous other alterations in the body. In the leucemias there is a permanent but variable increase in the number of circulating white blood cells, definitely associated with alteration of spleen, lymph nodes, bone marrow and other organs. For the sake of classification and discussion, two great forms of leucemia are recognized, namely, the lymphoid or lymphatic leucemia, sometimes called leucemic lymphadenosis, and the myeloid or splenomyelogenous leucemia, sometimes referred to as leucemic myelosis. These are further subdivided into acute and chronic varieties. It must be recognized, however, that border line cases occur in which it is difficult to say positively whether the disease is myeloid or lymphoid, acute or chronic. Furthermore, cases appear in which all the pathological signs are present except the increase in the number of circulating white blood cells. These are spoken of as aleucemic phases, which as a rule, probably represent the earlier stages of the disease but may appear as intermissions or as terminal stages. The outline given below must therefore be regarded as representing typical cases, in which the distinction of form is not difficult. For the sake of clarity, the chronic forms are discussed first.

Chronic Lymphoid Leucemia.—This is less common than the myeloid form and affects particularly people in middle and advanced life. It is more common in males than in females. The onset is gradual with progressive loss of strength and signs of anemia. The patient usually notices enlargement of

the superficial lymph nodes, although this may be much delayed. In addition to the general symptoms of anemia there may be gastro-intestinal symptoms, and in many cases there are short periods of fever with exacerbation of general symptoms and signs. The physical examination shows enlargement of the superficial lymph nodes and often of important groups of deeper lymph nodes, associated with enlargement of the spleen. The white blood cells commonly range between 60,000 and 100,000 per cmm., but may reach 1,000,000 or more. From 80 to 90 per cent. or more of these cells are lymphocytes and of these the vast majority are small lymphocytes. Although the polymorphonuclear cells are reduced in proportion, it is unusual that they are reduced in absolute number. Myeloid cells may sometimes be found, but if so only in small numbers. There may or may not be an anemia which, in more moderate degrees, is of secondary type with a low color index, but in the more severe degrees may show a high color index with anisocytosis, poikilocytosis and nucleated erythrocytes. The blood is increased in volume and in viscosity and in those cases where the number of lymphocytes is extremely large, may have a pale yellow color.

The pathological anatomy is fairly characteristic. Grossly, the lymph nodes of the body are likely to be distinctly enlarged throughout. They are pale, firm, and usually are discrete within each group. The tonsils and the lymphadenoid tissue of the intestines, as well as other lymph nodes, may be affected. Rarely, the thymus is involved (Major). Histo-

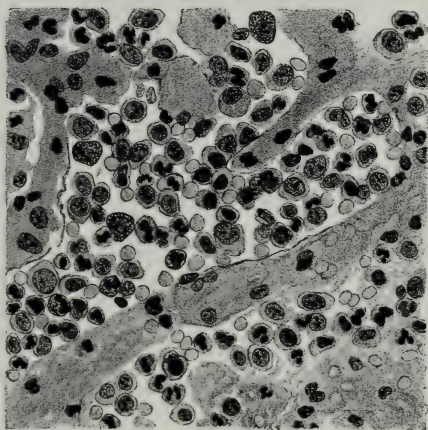


FIG. 225—Infiltration of liver in lymphoid leucemia.

logically, the architecture is more or less obscured by extreme multiplication of lymphocytes, although the follicles may be clearly defined. In the more chronic cases a slight fibrosis may appear. Mitotic figures are unusual and vascularization is not abnormal. The spleen is moderately or considerably enlarged, weighing usually from 500 to 1000 grams, although in our experience two spleens of over 2000 grams have been observed. The connective tissue of the spleen is increased more particularly in the capsule and trabeculae. The cut surface is relatively firm and sometimes shows considerably enlarged follicles, although this is by no means constant. Infarcts are also sometimes found. Histologically, the more or less marked fibrosis is observed, the follicles may or may not be enlarged, sometimes with enlargement of the germinal center, and the pulp shows a very marked increase of lymphocytes throughout. The bone marrow may or may not be seriously involved. In more severe cases the marrow of the shafts of long bones may be grossly of distinctly gray or reddish-gray color. Histologically, this shows islands of hyperplastic lymphogenic tissue, associated in the more severe cases of anemia with some hyperplasia of the erythroblastic centers. Although more common in acute

lymphatic leucemia, nevertheless, the chronic form may show lymphomata in various organs, particularly liver, kidneys and lungs. These are lymphoid nodules varying from microscopic size to grossly visible tumor-like masses exceeding a centimeter in diameter. These nodules are only fairly well circumscribed, relatively soft and with a slightly bulging, gray cut surface. Microscopically, they are poorly vascularized masses of lymphocytes which grow through connective tissue spaces pushing apart the parenchymatous elements. They are infiltrative rather than destructive and apparently originate in minute foci preëxisting in the tissue. Somewhat similar nodules may appear in the skin. If the anemia be pronounced there may be cloudy swelling and fatty degeneration of the parenchymatous viscera. A disposition to hemorrhage into the organs is less pronounced in chronic than in acute lymphatic leucemia.

Chronic Myeloid Leucemia.—This is a disease of the blood and myeloblastic apparatus, characterized by an increase in the number of circulating myelocytes and cells of the myeloblastic series. The disease is of gradual onset, with progressive loss of flesh and strength, and abdominal swelling due to enlargement of the spleen. Hemorrhage, gastro-intestinal disturbance, respiratory symptoms such as dyspnea and cough, fever and other symptoms and signs may be present. Examination of the blood shows as a rule 100,000 to 500,000 white blood cells but counts of 1,000,000 to 1,500,000 and more have been recorded. Of these cells from 60 to 90 per cent. are myelocytes, polymorphonuclear leucocytes and a small number of transition forms between the two. The cytoplasmic granulation of these cells is principally neutrophilic although there is a distinct increase in the basophilic cells and an absolute but not always a relative increase in the eosinophilic cells. Of these granular forms, the adult type of leucocyte usually preponderates over the myelocytes and myeloblasts, but collectively there is an enormous absolute increase in number. Although the lymphocytes may be proportionately reduced, nevertheless, they are considerably increased in absolute numbers and there is a relatively large proportion of large lymphocytes. Anemia is usually fairly well marked and is of secondary type with a low color index. In the more severe anemias the red blood cells may show anisocytosis and poikilocytosis. Regardless of whether or not there is an anemia, nucleated erythrocytes are almost always found. The number of platelets is also increased. There is an increase in volume and in viscosity of the blood (see Minot, Buckman and Isaacs).

The most striking features of the pathological anatomy are changes in the spleen and bone marrow. The spleen is usually enormously enlarged (the largest chronic splenomegaly—Kaufmann) attaining weights of 2000 and 3000 grams and even up to 10,000 grams. The organ is large, dark red and, depending upon the duration of the disease, shows increase of connective tissue, sometimes with adhesions to surrounding organs. The capsule may be thin and tense but usually is thick, dense, opaque, and sometimes hyaline, and the trabeculae and other connective tissues of the spleen are also increased. The cut section usually shows no follicles but a definite increase of connective tissue with a general

gray or yellowish-gray tint to the red color of the pulp. The latter is of normal or firm consistence and may show numerous small foci of necrosis. Microscopically, the spleen is converted into a myeloblastic organ. The follicles are small and often cannot be made out at all. The pulp shows large numbers of myelocytes and leucocytes of the various orders. Lymphocytes are usually present but are often obscured by the granular cells. Nucleated red blood corpuscles are sometimes found but usually not in large numbers. Megakaryocytes, sometimes exhibiting phagocytosis, are also found. Pigmentation is not increased. The bone marrow shows an enormous myeloblastic hyperplasia. The marrow in the shafts of the long bones has a semisolid or diffuent

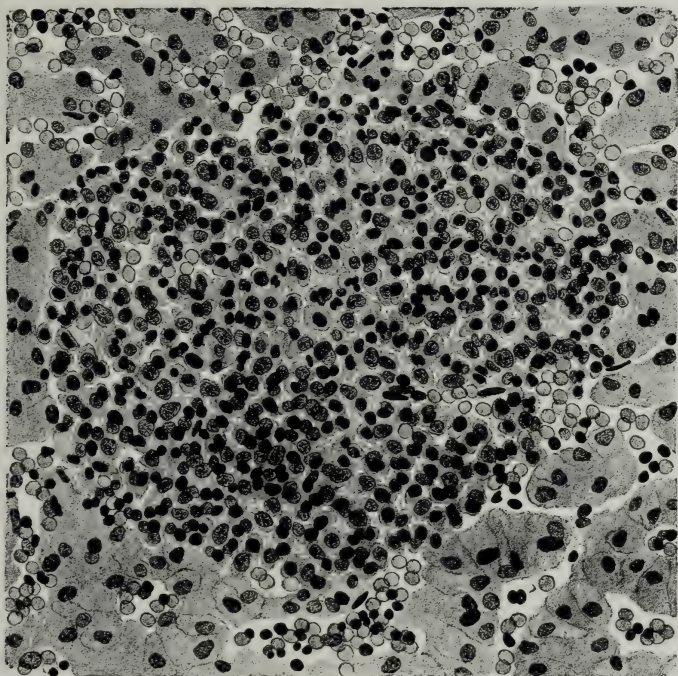


FIG. 226—Infiltration of liver in myeloid leukemia.

consistence and is of grayish-yellow color, so much resembling pus that the bone marrow is often spoken of as pyoid. Histologically, the bone marrow is made up principally of myelocytes and leucocytes, but non-granular cells are also encountered which for the most part are myeloblasts. Lymphogenic foci are usually absent. Erythroblastic activity is present but not marked. The megakaryocytes are large and numerous. There is little phagocytosis of cells and fragments and little or no pigmentation; mitotic figures may be prominent, more especially in the myeloblasts. The liver is usually considerably enlarged, sometimes attaining a weight of 5000 grams or more. The organ is firm, with somewhat rounded edges and tense capsule and in the cut surface sometimes shows, even grossly, minute foci of gray color representing infiltration in the periportal spaces. Microscopically, the periportal spaces usually

are much enlarged by a rich infiltrate of myelocytes and of leucocytes. In addition, all the blood spaces show large accumulations of these cells. This engorgement of capillaries by blood rich in myelocytes and leucocytes is practically constant throughout the body. The skin very rarely shows focal infiltrates grossly similar to those of lymphatic leucemia. In myeloid leucemia, however, the rule is for diffuse infiltration of tissue rather than the formation of tumor-like nodules as in lymphoid leucemia. If the accompanying anemia be pronounced, there is cloudy swelling and fatty degeneration of the parenchymatous viscera. In spite of poor extravascular clotting, thrombosis may be observed in various situations, sometimes with infarction. Thrombosis of veins draining the penis may lead to persistent priapism (Ruh).

Acute Leucemias.—Whereas the chronic leucemias run a course lasting over several months or years, the duration of the acute leucemias is measured rather in weeks and months. The symptoms develop more rapidly and are oftentimes much more severe. Fever is likely to be a more prominent symptom than in the chronic form. Hemorrhages also are more frequent and more severe. The essential changes in the tissues are much the same in both chronic and acute forms of each type of disease except that in the case of acute lymphoid leucemia the formation of lymphomata is more pronounced than in the chronic form. Whereas the chronic forms attack individuals of early and late middle life the acute forms are diseases of earlier life and indeed occur in childhood. The total number of circulating white blood cells is not likely to be so great as in the chronic form, figures ranging between 40,000 and 80,000 being the usual ones. Differentiation between the two acute forms on the basis of blood examination is sometimes extremely difficult because of the occurrence of immature cells of either the lymphoblastic or myeloblastic order. These two types of cells are essentially the same morphologically, being large mononucleated cells with non-granular cytoplasm. They may constitute 80 to 90 per cent. of the circulating white cells in either myeloid or lymphoid leucemia. Minor points of distinction between these cells have been described but are unsatisfactory from the practical point of view. It has been found, however, that the non-granular cells of the myeloblastic series contain oxydase granules which may be demonstrated by the original or some modification of the Schultze method. If, therefore, the non-granular cells give the oxydase reaction, the leucemia is to be classified as an acute myeloid leucemia. If they do not, it is of the lymphoid variety. Clinical examination, however, is of great importance in establishing the diagnosis. At the autopsy the difference in character of spleen, bone marrow, liver and lymph nodes usually establishes the final diagnosis beyond any question, because in the lymphoid forms there is the lymphoid hyperplasia of spleen and lymph nodes, bone marrow and very frequently lymphomata of the various viscera, whereas in the acute myeloid form, the myeloid metaplasia of the spleen is apparent as is also the myeloid hyperplasia of the bone marrow. Connective tissue hyperplasia of such organs as spleen, lymph nodes and liver is neither so common nor so severe as in the chronic varieties.

Chemistry.—Much attention has been given the chemistry of the leucemias, but the most definite results have been obtained in the myeloid forms, probably because of the rich content of ferments in cells of the myeloid series. It is true that bone marrow of lymphatic leucemia placed aseptically on gelatin plates may show slight proteolytic activity, but this is probably due to some myeloblastic activity since the other organs are not proteolytic and the blood shows none of the products of protein decomposition. In myeloid leucemia the spleen, lymph nodes and bone marrow are proteolytic and the blood shows an increase of non-coagulable protein, presumably made up in large part of proteoses. The disintegration of the nuclei of the cells in the blood and tissues, resulting at least in part from ferment activity, may lead to the appearance in the urine of decomposition products of nucleoproteins such as uric acid, purine bases and phosphoric acid. As a result of autolysis of cytoplasm and nuclei, proteoses, amino-acids and the products just enumerated may appear in the blood and urine. Charcot-Leyden crystals, probably derived from the nucleoproteins, may occur in the blood and various tissues. In concordance with these facts metabolism is also more increased in myeloid than in lymphoid leucemia. Clotting of the blood is likely to be delayed and incomplete, especially in myeloid leucemia. No satisfactory explanation is to be offered except that in one case Whipple found an excess of anti-thrombin. The whole problem of the chemistry of these diseases is admirably discussed by Wells.

The Nature of Leucemia.—Aside from the age and sex incidence of leucemia as mentioned above, there is little in the human pathology of this disease to indicate clearly its cause. In certain of the cases traumatism precedes the occurrence of symptoms, and it is at least possible that such trauma may provide a portal of entry for some infectious agent. There are, however, no satisfying reports to indicate clearly that human leucemias are infectious in nature. The studies of Ellerman and of Schmeisser demonstrate clearly the infectious nature of leucemia of the fowl, and Ellerman maintains that the causative organism is a filterable virus. The same agent may produce in one animal a myeloid type and in another animal a lymphoid type of leucemia. Apparently, then, the manifestations of the disease represent alterations of reaction rather than of cause. These observations, however, are not yet applicable to man. The fact that the diseases represent an almost unlimited growth of cells in the hematopoietic system and blood, gives the condition a tumor-like character. In the myeloid form of the disease there is infiltration of various connective tissue spaces and of blood vessel walls. The same is true in lymphoid forms and, in addition, the lymphomata although not highly destructive are nevertheless distinctly infiltrative. Much emphasis has been placed on these facts, particularly by the German writers, who are disposed to regard leucemia as a tumor of the blood and blood forming apparatus. There is, however, no clear indication that metastasis occurs other than can be explained by the presence of large numbers of migratory cells within the circulation. The exact nature of the leucemias therefore awaits further investigation.

Extraneous Substances in the Blood.—The dissolved pigments of the blood include particularly bilirubin, but others such as methemoglobin also occur. Solid pigments include the pigment granules of malaria and more rarely crystals of bilirubin, and also carbon particles which gain access presumably through lymph nodes. Air in the blood must be regarded as a foreign body as has been discussed in connection with air embolism in the chapter on the general pathology of circulation. The same is true of fat when the globules are sufficiently large to occlude blood vessels. It is not to be forgotten, however, that fat occurs normally in the blood and may be found as a fine emulsion in fairly large quantities in cases of lipemia. Substances such as uric acid, urates, glycogen, sugar, creatinine, etc., may, under various circumstances, accumulate in pathological amounts in the blood.

Parasites.—The most important and common is the plasmodium malariae which has its asexual cycle in the human blood and perhaps under certain circumstances may go through a sexual cycle. Others of importance include the filaria sanguinis hominis, the distomum hematobium, various forms of trypanosomes, especially that of African sleeping sickness, and larval forms of the trichinella spiralis. Spirilliform parasites include particularly the spirillum of recurrent fever and the spironema pallidum of syphilis. Various bacteria appear in the circulating blood as a part of subinfection or of septicemia.

THE SPLEEN

Congenital Anomalies.—Very rarely in association with general malformations, the spleen may be absent; this may even occur in individuals who are otherwise normal, without interfering with growth and development. Congenital variations in size also occur so that the spleen may be either extremely small or considerably larger than normal. A certain amount of lobulation of the spleen, particularly in the form of linear depressions in its margin, is not uncommon. Accessory spleens are not rare, appearing as small globular bodies, especially in the gastrosplenic ligaments. These resemble lymph nodes but have the characteristic color of the spleen and participate in the pathological processes of the spleen. Histologically, their structure is characteristic. In malformations where the abdominal cavity is not closed, ectopia of the spleen may be observed.

Alterations of Position.—The spleen may be pushed upward by swellings within the abdominal cavity such as are produced by ascites, abdominal tumors and pregnancy. The spleen may be pushed or pulled downward by the weight of considerable enlargement or its ligaments may be stretched by tight lacing and by conditions such as ascites, tumors and pregnancy, which after their removal leave relaxed ligaments. Such floating spleens usually become the seat of passive hyperemia and become chronically enlarged. Sometimes the pedicle becomes twisted and the spleen strangulated. Adhesions may fix the organ in abnormal position.

Retrogressive Processes.—Of the various degenerative and infiltrative processes of the spleen, amyloid is by far the most important. This may be an

isolated occurrence in the spleen but is more commonly associated with amyloid of other organs, and in any case is due to the usual causes of amyloid. Two grades of amyloid exist, namely, that involving the follicles, the *sago spleen*, and the more diffuse form sometimes called the *bacony* or *lardaceous spleen*. In the former the spleen is moderately enlarged and firm, usually without thickening of the capsule. The cut surface is firm, of red color, and shows small glassy hyaline areas, corresponding in size to enlarged follicles, which transmit the underlying red color of the organ. Special stains such as iodine or the iodine and sulphuric acid process, demonstrate the characteristic reaction in the foci of the amyloid. In diffuse amyloid the spleen is likely to be larger although it rarely exceeds a weight of 500 to 600 grams. The appearance is much the same as in the *sago spleen*, except that in the cut surface the glossy or gelatinous character is considerably more diffuse. Similarly, the reaction to the special stains is also diffuse. Fibrosis is not common but if present is more pronounced in the diffuse than in the focal amyloids. Histologically, the amyloid is found in the central arterioles and in the substance of the follicles, associated with reduction in number of cells. In the diffuse forms, in addition to the follicular involvement, the hyaline material occurs also in the reticular substance and the walls of the vascular sinuses. Miliary or larger tubercles may be present.

Hyaline degeneration of the central arterioles of the spleen is very common and in people past middle life is almost constant. This is differentiated from amyloid by the fact that it is confined to the arterioles, and also by special staining. Hyalin may also appear in the capsular substance and in the trabeculae as well as in the reticular connective tissue. Necrosis of the spleen occurs most commonly in connection with infarction. In infectious diseases and *status thymolympathicus*, the germinal centers of the follicles may show considerable hyperplasia, and especially in children there is likely to be necrosis of the germinal centers, sometimes with the formation of small hyaline necrotic masses. Atrophy of the spleen occurs in old age and in connection with exhausting diseases such as anemias and malignant tumors. The organ is reduced in size, firm in consistence, and usually shows overgrowth of connective tissue throughout. Since the atrophy affects especially the lymphoid parts of the spleen the color is usually paler than normal. Various pigmentations of the spleen are of common occurrence. Hemosiderin is practically always present in small amounts in adult spleens, occurs in larger quantities in cases of secondary and primary anemia and is often seen around the borders of infarcts. Hematoidin is likely to appear within the necrotic tissue of infarcts. Malarial pigment is common also. Calcification may result from necrosis as of infarction, in tuberculosis, in arteriosclerosis, in the formation of phleboliths and as a part of syphilitic involvement to be described subsequently.

Circulatory Disturbances.—Anemia of the spleen is usually the result of a general anemia. Unless enlarged because of blood destruction, the organ is usually somewhat reduced in size, of firmer consistence than normal and pallid both on the outer and cut surfaces. The relationship of the spleen to anemias offers problems along the line of blood formation, blood destruction,

iron metabolism, influence upon the bone marrow and lymph nodes, etc., but for these the reader is referred to Pearce, Krumbhaar and Frazier.

Active hyperemia of the spleen is a common occurrence physiologically, especially during the process of digestion. It also occurs pathologically in connection with a wide variety of acute infectious diseases and is in part responsible for the enlargement of the spleen noted in these conditions, both clinically and pathologically. Passive hyperemia is also extremely common, incident to chronic heart and lung disease, local passive hyperemia due to disease of the liver, and due to obstruction of the portal vein either by thrombosis or com-



FIG. 227—Large healed infarct of spleen.

pression. In cases of passive hyperemia of short duration, the organ is moderately enlarged, of medium consistence and with a tense capsule. The cut surface is of dark red color, bulges and bleeds freely. There is no important change in connective tissue incident to the hyperemia, but the follicles are usually obscured by the soft red pulp. Microscopically, the organ is characterized by an extremely rich content of erythrocytes and a minor grade of hemosiderin pigmentation. The follicles are of normal or somewhat reduced size. As the duration of hyperemia increases, connective tissue overgrowth becomes more conspicuous and the spleen correspondingly firmer. The organ may attain a weight of 200 or 300 grams or more, and shows a somewhat thickened, opaque, slate colored capsule. The organ cuts with increased resistance and shows a fairly firm,

dark red or purple cut surface which becomes a brighter red color upon exposure to the air (cyanotic induration). It bulges slightly and bleeds slightly. The follicles may or may not be visible. The trabeculae are increased in size and are visible grossly as irregular bands of dense connective tissue. Microscopically, the connective tissue hyperplasia is particularly apparent in capsule and trabeculae but also involves the reticular substance. Large quantities of blood are present and hemosiderin pigmentation may be conspicuous. Later stages of passive hyperemia are likely to show a somewhat shrunken spleen, due particularly to the contraction of the hyperplastic connective tissue, representing a cyanotic atrophy. The organ is normal or reduced in weight with a thick opaque, slate colored capsule and a retracting, firm, dark red or somewhat slate colored cut surface with extreme prominence of the connective tissue trabeculae. Certain special forms of passive hyperemia of the spleen will be considered subsequently with the splenomegalies.

Embolism of the splenic arteries and its branches occurs particularly as the sequence of valvular disease of the heart, but may be due to any of the other causes of arterial embolism. The main branch of the splenic artery may be occluded, followed by complete necrosis of the spleen. Smaller infarcts of the spleen follow the usual course of the process. At first they are swollen, dark red, hemorrhagic, solid, conical areas which subsequently undergo necrosis and decolorization to become white infarcts. As the process advances, the central substance becomes more and more necrotic and there is reactive fibrosis in the margin, and shrinkage of the entire area. Microscopically, the connective tissue architecture of the spleen may be apparent in the infarct even after necrosis is well advanced. In the earlier stages necrosis is associated with extensive hemorrhage in the area, and in the later stages the necrosis may be accompanied by a considerable deposition of hematoidin. Ultimately, the infarcts may be converted into dense fibrous scars which are sometimes confused with congenital lobulations of the organ. If the embolism be of infectious nature, abscesses of the spleen occur. At first these are of typical conical shape but subsequently may enlarge and show no morphologic character to indicate their origin.

Hemorrhages of the spleen are likely to occur in connection with the enlargement incident to acute infectious diseases. Grossly, they appear in the spleen as irregularly disposed and shaped areas of dark red blood. Sometimes the spleen may rupture, with serious hemorrhage into the abdominal cavity. This occurs only rarely in connection with acute infectious diseases and is usually caused by traumatic injury.

Thrombosis of the splenic vein may be due to inflammatory lesions along the course of the vein, such as ulcer of the stomach, tumors, inflammatory lesions of the pancreas, may be due to compression or other involvement by tumors and is likely to occur as the result of twisting of the pedicle of a floating spleen. This produces considerable enlargement of the spleen of the order described above in connection with the more acute forms of passive hyperemia. Emboli and thrombi may become organized and ultimately calcified. These

phleboliths are extremely common as hard, pearly nodules in the substance of the spleen. They are circumscribed, two or three millimeters in diameter and may be confused with calcified tubercles or small tumor nodules.

Acute Hyperplasia.—This is sometimes referred to as acute hyperplastic splenitis and as acute splenic tumor. Although not constantly present, it is one of the commonest postmortem indications of acute infectious disease. The response to various infections is different in degree and in certain special characters. The hyperplasia is believed to follow the acute hyperemia of the spleen in infectious diseases. The spleen of acute hyperplasia may attain weights of 500 or 600 grams or more but in other instances may be enlarged only slightly beyond the normal. The moderate degrees may be of firm consistence but the more severe cases show a soft, pulpy consistence. The capsule is thin and tense. The organ cuts with normal resistance and shows a bulging red, bluish-red or reddish-gray, pultaceous or pulpy cut surface, from which a considerable amount of diffuent material may be scraped. The firm spleen shows a relatively firm cut surface. The swelling of the pulp is likely to obscure all markings by follicles or connective tissue trabeculae. Histologically, the connective tissue is normal in amount but may appear to be reduced because of the increase in cellular content. In many cases the follicles are of normal size but in others, more especially in diphtheria and scarlatina, when occurring in childhood, the follicles are somewhat enlarged because of hyperplasia affecting particularly the germinal centers which may also be the seat of a small amount of necrosis. The pulp shows a rich or moderate content of blood and a considerable increase in the number of lymphocytes and endothelial cells, the latter originating for the most part from the endothelium of the sinuses. Polymorphonuclear leucocytes may be present in considerable numbers, more especially in septicemia and pyemia. Fatty degeneration of the hyperplastic endothelial cells may also be present, especially in septicemia and pyemia. The endothelial cells are likely to be phagocytic for fragments of other cells, particularly lymphocytes and red blood corpuscles, nuclear fragments and hemosiderin. This feature is often prominent in typhoid fever. Hemorrhage into the substance of the spleen may also occur, especially in plague and anthrax. Small areas of necrosis of the pulp are not uncommon, especially in the later stages of acute hyperplasia, which probably accounts for the softer consistence of the organ in later stages. Typhoid fever and plague produce the most constant and greatest acute hyperplasia of the spleen. Other diseases which may produce considerable enlargement, but may also produce little noticeable change, include anthrax, acute miliary tuberculosis, septicemia, and pyemia. Scarlatina, diphtheria and pneumonia are not likely to produce great enlargement, although in the last disease the spleen may be larger after the crisis than before. Following recovery, the spleen may be completely restored to normal, although in most cases it seems likely that there is some residuum in the form of fibrosis of the capsule and trabeculae and perhaps hyalin of the central arterioles. Evans divides the acute hyperplasias into a red and a gray variety, the former occurring in typhoid fever with marked hyperemia

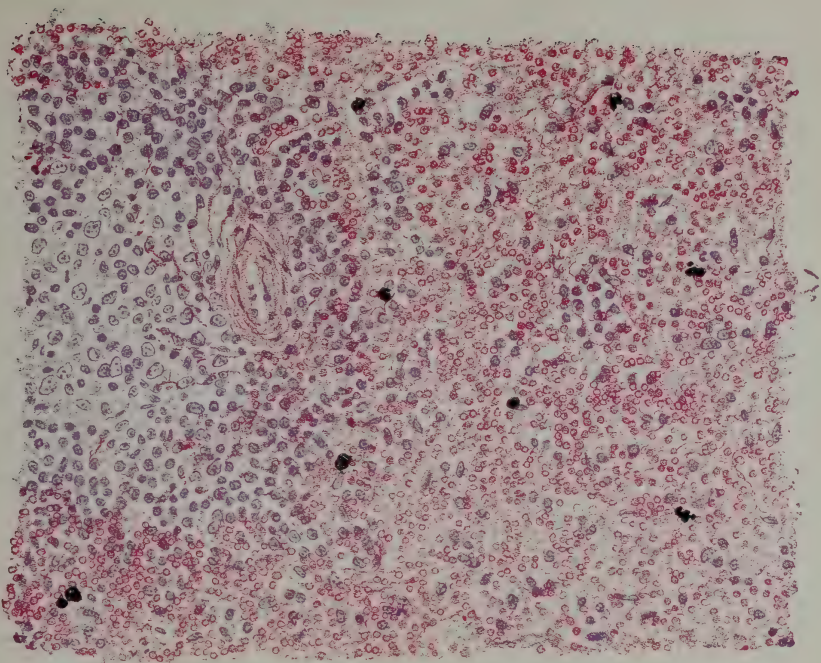


PLATE XII—The spleen in congenital hemolytic icterus, showing congestion and pigmentation. From Pearce, Krumbhaar and Frazier, The Spleen and Anemia.

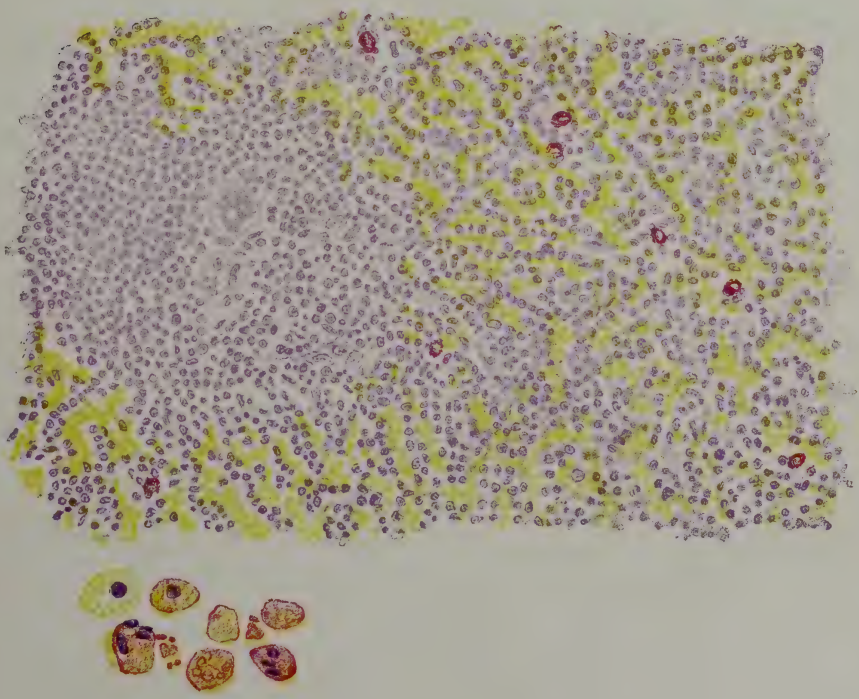


PLATE XIII—The spleen in pernicious anemia, showing detail of phagocytosis of erythrocytes and pigment. From Pearce, Krumbhaar and Frazier, The Spleen and Anemia.

of the spleen and the latter in such diseases as pneumonia and septicemia, where there is marked cellular hyperplasia. The distinction is not constant.

Abscess of the spleen is most commonly the result of infected emboli but may also be due to extension from neighboring processes such as gastric ulcer, perirenal abscess, abscess of pancreas, pylephlebitis and infection of traumatic hemorrhage. The gross and microscopic features do not differ from those observed elsewhere.

Chronic Hyperplasia.—Although the term splenomegaly is sometimes applied to acute hyperplasia, as a rule it is limited to the chronic hyperplasias. Chronic hyperplasia of the spleen may be due to such chronic infectious diseases as syphilis, tuberculosis, malaria, kala-azar and other tropical diseases; may be due to blood diseases such as leukemia; may be due to passive hyperemia including that incident to cirrhosis of the liver, and may be a part of certain diseases whose nature is not well known but which almost constantly exhibit enlargement of the spleen. The chronic enlargement may, in the early stages, be due very largely to the hyperplasia of the cellular content of the spleen with a moderate involvement of the connective tissue, but in the later stages the connective tissue predominates and the cellular part may be the seat of considerable atrophy. The more common forms of splenomegaly show only moderate enlargement. The organ has a thick, dense, slate colored, opaque capsule. It is firm, cuts with increased resistance and shows a non-bulging, light or dark red, firm cut surface with preponderance of connective tissue. Histologically, there is a considerable overgrowth of connective tissue which in some instances affects principally the capsule and trabeculae, in others principally the connective tissue of the reticulum, and in others, both. The follicles may or may not be enlarged. The central arterioles are usually the seat of hyaline change. The lymphocytes are usually increased and, in addition, in special forms of splenomegaly other cell characters are observed. These will be considered under the heading of the separate diseases which appear to be worthy of mention.

Malaria.—In the more acute forms of the disease, enlargement of the spleen may be that of acute hyperplasia, characterized by the presence histologically and even grossly of the malarial pigment. The parasites may also be discovered in the blood. The chronic splenomegaly of long standing malaria constitutes the so-called "ague cake." The organ may be considerably enlarged, attaining weights of 1000 grams or more. It is firm, and shows a thick, opaque, slate colored capsule which is sometimes adherent to the surrounding structures. The organ cuts with distinctly increased resistance, and shows a

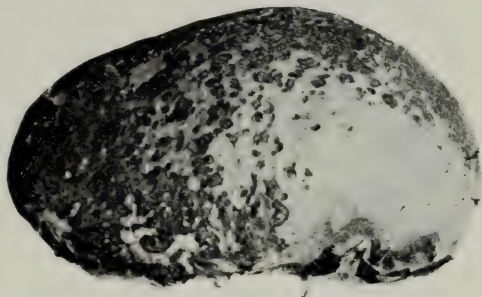


FIG. 228.—Chronic hyperplasia of spleen (malaria) with chronic hyalocapsulitis (zuckerguss). Army Medical Museum 30190.

firm, non-bulging, brownish-red or brown cut surface in which the trabeculae are prominent. Microscopically, in addition to the fibrosis of capsule and trabeculae, there may be moderate fibrosis of the reticulum and there is almost constantly a considerable number of minute, dark brown granules which do not give the iron reaction. These are for the most part in endothelial cells but may be found in extracellular positions.

Kala-azar, an infectious disease of Oriental tropical countries, caused by the *Leishmania donovani*, shows recurring fever, gradual loss of flesh and strength, secondary type of anemia and enlargement of spleen and liver. The careful studies of Meleny make it apparent that the pathological changes are essentially due to proliferation of cells of the reticulo-endothelial apparatus in liver, spleen, lymph nodes and bone marrow, due to invasion by the parasite. The organisms enter the cells and multiply and the process seems to be practically an invasion rather than the usual type of phagocytosis. Capillary endothelium may be invaded and react; even the parenchymatous cells of the liver may contain parasites. The spleen is large, firm as the result of endothelial hyperplasia and hyperemia rather than fibrosis, and dark red. The follicles are small and the special feature is the large number of invaded endothelial cells both mononuclear and multinuclear, whose cytoplasm is filled with large numbers of organisms. These are minute bodies, about the size of a blood platelet, with clear cytoplasm and usually two very minute chromatin masses.

Giant lymph follicle hyperplasia is a disease of unknown origin which affects lymph nodes and spleen. The latter may attain a weight of 1800 grams or more (Brill et al.). The follicles of the spleen may be several millimeters in diameter and project as gray, well defined nodules in the cut surface. Microscopically, there is marked hyperplasia of the central large cells of the follicles.

Blood Diseases.—The spleen of leucemias and of the more common varieties of anemia has been described in the section on diseases of the blood. The spleen of the so-called splenic anemia simply shows the picture of a chronic splenomegaly without any special character features. As a matter of fact, splenic anemia is probably not a separate disease entity and may be related either to Banti's disease or some other similar condition. While admitting this, Rolleston thinks that arguments are equally strong for regarding splenic anemia without liver enlargement as a separate entity. Chronic types of splenic enlargement may also occur in connection with infantile types of anemia and with hemolytic jaundice.

The spleen may be moderately enlarged in hemochromatosis where there is a fibrosis in association with pigmentation.

Banti's Disease.—Whether this be a separate disease or simply a symptom complex or syndrome, numerous cases are on record showing the particular combination of symptoms and signs. The essential features are enlarged spleen, anemia of chlorotic or secondary type, hepatic cirrhosis, and acites, developing in progressive stages. Much discussion has been presented concerning the nature of the disease, but it is probable that the primary change is in the spleen and that this is associated with increased blood destruction,

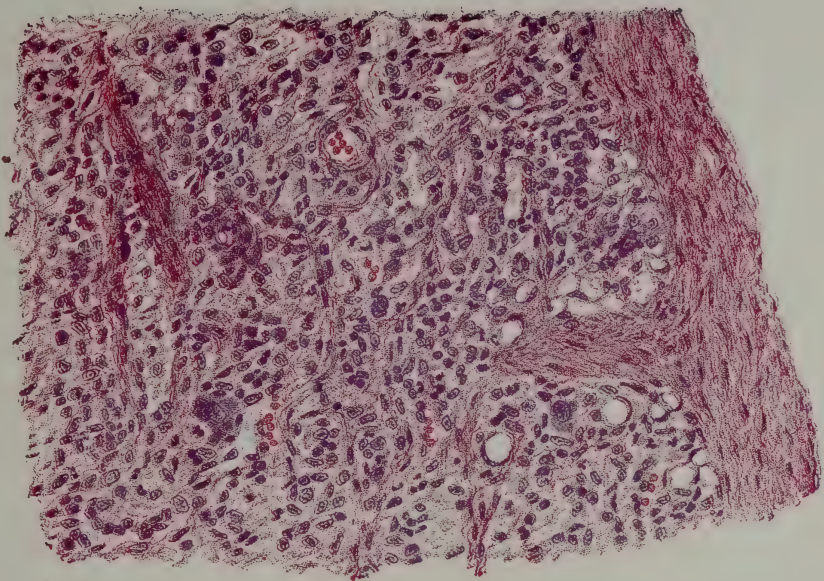


PLATE XIV—Reticular hyperplasia of spleen in early Banti's disease. From Pearce, Krumphaar and Frazier, The Spleen and Anemia.

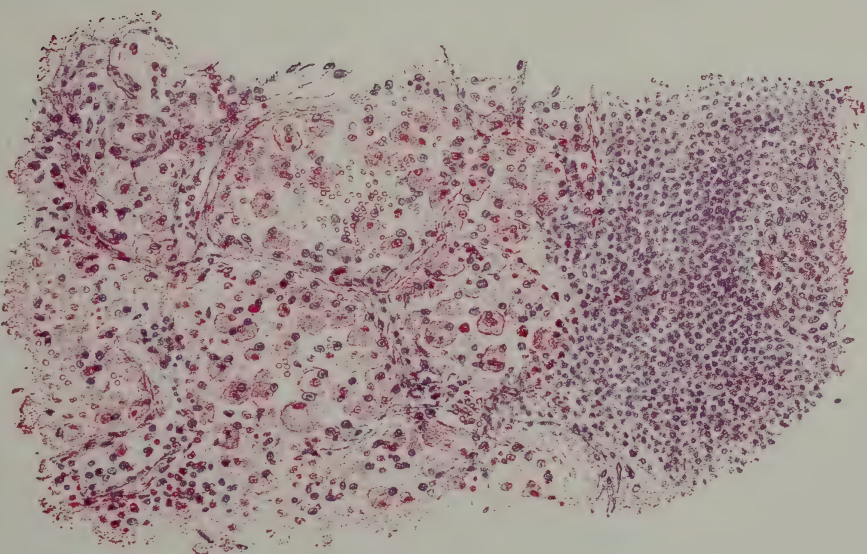


PLATE XV—Alveolar arrangement of characteristic cells in the spleen of Gaucher's disease. From Pearce, Krumphaar and Frazier, The Spleen and Anemia.

without adequate compensatory hyperplasia in the bone marrow. The liver is at first enlarged but subsequently shows all the features of the ordinary perilobular type of hepatic cirrhosis. The involvement of the liver is probably secondary to the condition in the spleen. Following the development of the atrophic cirrhosis of the liver, ascites develops. No definite cause has been established, although Warthin believes that the condition is due to an infectious thrombophlebitis of the portal or splenic vein. Symmers regards syphilis as a cause. The spleen is the seat of a chronic splenomegaly which has no especial character except that the hyperplasia of the reticular connective tissue may be especially prominent. Endothelial phagocytes containing fragments of red blood corpuscles and hemosiderin may also be found (see Dürr).

Splenomegaly with Lipoid Deposits.—Deposit of certain lipoids or groups of lipoids may be especially manifest in the spleen. In two diseases, namely Gaucher's disease and Niemann's disease, splenomegaly may be pronounced.

Gaucher's disease may begin in early or middle life, runs a prolonged course, sometimes of many years, often without serious disability. In later stages, secondary anemia of chlorotic type and leucopenia occur. The enlargement of the spleen, a chronic splenomegaly, is characterized microscopically by the presence of many large mononuclear, or sometimes multinuclear, cells, with small, dense, sometimes wrinkled nuclei and rich, finely vacuolated cytoplasm. Cell masses may be found in enlarged follicles. In the pulp they are widespread but may form foci; some of which seem to be in sinuses. The cells are derived from the reticulo-endothelial system, and according to Mandlebaum and Downey may be of elongated form with somewhat fibrillated cytoplasm. These authors question the lipoidal nature of the cytoplasmic contents, but the studies of Epstein and of Lieb indicate that the substance is one of the cerebrosids. It is now generally accepted that in Gaucher's disease these cells are found only in the hematopoietic system.

Niemann's disease occurs in infancy or early childhood, is sometimes familial, shows failure of proper development, anemia and a leucocytosis with relative increase in lymphocytes, large spleen and liver, and runs a rapid course terminating in death within the first two years of life. The subacute splenomegaly is characterized histologically by the appearance of cells similar to those of Gaucher's disease, but more definitely rounded and with somewhat larger vacuoles. Wahl and Richardson's study of the cases reported by Knox, Wahl and Schmeisser indicate that the material is in the lecithin group, but Pick's more recent study shows it to be principally phosphatids. The deposit or storage of this material in reticulo-endothelial cells may be widespread in the body, affecting not only the hematopoietic system but also other organs such as adrenal, kidney, aorta, lungs (Bloom). Storage of other lipoids and lipins in these cells is discussed with the reticulo-endothelial system.

Hodgkin's Disease has been considered in the chapter on infectious granulomata. In addition to the general phenomena in the lymph nodes and circulating blood, the spleen is likely to be slightly or moderately enlarged but may

uncommonly attain a weight of 1800 grams or more. It may escape involvement or in some rare cases appear to be the only organ attacked. The capsule is usually tense and smooth, but its thickness and opacity depend upon the stage of the disease and the degree of fibrosis, which increases as the disease progresses. Similarly, the consistence may be normal or extremely firm. The character of the cut surface also varies with the degree of fibrosis, in the later stages showing considerable overgrowth of the trabeculae and reticular tissue. It may be mottled gray because of foci of cell hyperplasia, and gross areas of necrosis may occur. Histologically, the condition is characterized by variable degrees of fibrosis throughout the spleen, usually with reduction in the size of the follicles and diminution in distinctness of their outline. There may be a number of endothelial cells in the follicles and occasionally small areas of hyalin are noted. Frequently, they are replaced by the Hodgkin's granuloma. The pulp is more or less replaced by a mixture of cells comprising the typical mononuclear or multinuclear giant cells, many endothelial cells, lymphocytes,

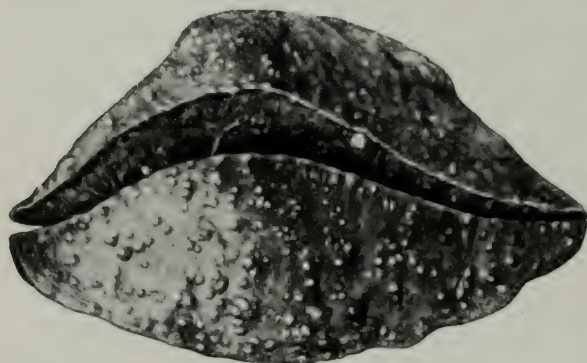


FIG. 229—Miliary tubercles of spleen projecting in capsule.

plasma cells and in many cases a considerable number of eosinophiles. Small foci of necrosis are likely to be encountered and pigmentation is common. The granuloma may invade blood vessels (Longcope).

Infectious Granulomata.

Syphilis.—Congenital syphilis may show some chronic hyperplasia of the spleen, principally due to connective

tive tissue overgrowth involving capsule, trabeculae and reticular substance. Gummata may also be encountered in congenital syphilis. *Spirochaeta pallidum* is often present in large numbers in the congenital lesion. In the secondary stage of syphilis the spleen may show a moderate acute hyperplasia. In later syphilis gummata may be encountered, but the more common change is a chronic hyperplasia due principally to overgrowth of connective tissue in which occasionally spirochaeta may be demonstrated. The thick capsule may show hyalinization. Symmers describes the occurrence in the spleen, grossly, of small ochre colored bodies which microscopically are found to represent small arteries, richly infiltrated with mineral salts and often surrounded by a small area of red blood corpuscles. This is believed to be due to syphilis.

Tuberculosis.—In addition to the acute hyperplasia which may accompany acute generalized miliary tuberculosis, the spleen is frequently the seat of tubercles of various forms and sizes. Acute miliary tuberculosis of the spleen is usually a part of generalized miliary tuberculosis. The organ is moderately or considerably enlarged, with a tense, thin, translucent capsule through which the miliary tubercles may be visible. The consistence may be firm

but sometimes soft and diffuent. In the cut surface the miliary tubercles appear as minute or larger, definitely rounded, solid, gray or pale yellow nodules which can easily be picked out on the point of a knife. They are to be distinguished from follicles because of the fact that follicles are of more definitely gray color and less sharply circumscribed. In later stages the tubercles may be encapsulated as a part of chronic miliary tuberculosis. Histologically, the spleen is likely to show all the features of acute hyperplasia and in addition the presence of typical miliary tubercles with minute necrotic centers and surrounding zones of endothelial and lymphoid cells and giant cells. Not infrequently they develop within the follicles. More particularly in children, acute or subacute tuberculosis of the spleen shows the presence of large numbers of small or larger conglomerate tubercles with extensive caseation of the centers. This resembles closely tuberculosis of the spleen as it occurs in monkeys. The



FIG. 230—Cut surface of spleen, the seat of acute miliary tuberculosis. Army Medical Museum 2713.

same condition may affect adults and appears to be more common in negroes than in whites. Very rarely a large solitary tubercle, the so-called tuberculoma, may be observed in the spleen. In by far the majority of instances, tuberculosis of the spleen can be easily demonstrated as secondary to tuberculosis in some other situation. There are cases, however, in which the primary focus is either not demonstrated or in such a state of quiescence as to be overlooked or regarded as insignificant. Winternitz has collected fifty-one cases of this sort. Without widespread tuberculosis, the involvement of the spleen appears to have little or no influence upon the hematopoietic system, but occasional cases of secondary polycythemia have been reported.

Tumors.—Of the primary benign tumors of the spleen the hemangioma is of the most importance. This is usually cavernous. It may appear as a uniform, more or less marked enlargement of the spleen or may be grossly of nodular character. Cases also occur in which the hemangioma is simply a small nodule within the otherwise normal spleen. Grossly, there is usually some overgrowth

of connective tissue of capsule and trabeculæ. The spleen is large and of spongy consistence; upon cutting, it bleeds freely and loses considerable weight. Microscopically, the character of cavernous hemangioma is clearly distinguishable. Other benign tumors which rarely occur include fibroma, chondroma, and osteoma. Primary sarcoma of the spleen is also rare (Bunting). Symmers describes an acquired telangiectatic splenomegaly not clearly neoplastic in character. Of metastatic tumors occurring in the spleen the sarcoma is far more frequent than the carcinoma. Of particular importance is the fact that in certain cases of lymphosarcoma the spleen may be the seat of considerable enlargement. Melanotic sarcomata also metastasize to the spleen. Secondary carcinoma of the spleen is extremely unusual. Kaufmann states that of 1078 cases of carcinoma only 0.7 per cent. show metastasis in the spleen. This is also emphasized by Sappington.

Small cystic projections may occur in the capsule of the spleen due to rupture of parts of the capsule, and extrusion of the splenic contents into this so-

called splenic hernia. Larger blood filled cysts may result from traumatism. Occasionally cysts of lymphatic origin may attain considerable size, and rare cases of polycystic degeneration are reported.

Parasites.—The most important metazoan parasite in human medicine is the echinococcus which may produce cysts of considerable size in the spleen. Kaufmann also mentions cysticerci and pentastomum.

Capsule of the Spleen.—The acute inflammations of the capsule designated

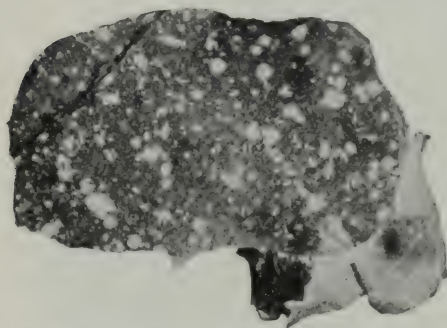


FIG. 231.—Cut surface of spleen of child, showing multiple conglomerate tubercles.

as acute capsulitis or perisplenitis are usually a part of local or general peritonitis, but may follow abscesses in the spleen and bland or septic infarction. Healing may produce fibrous adhesions to the diaphragm, abdominal wall and neighboring viscera, i. e., a chronic adhesive perisplenitis. Chronic fibrous perisplenitis may be the sequence of acute inflammations, but is more commonly the result of attacks of acute hyperplastic splenitis or due to chronic hyperplasias, tumors, parasites, etc. The fibrous thickening is accompanied by increasing opacity so that the underlying color of the spleen is poorly transmitted and the capsule appears to be slate colored. Hyaline degeneration of the thickened capsule is common and may be in the form of small, projecting nodules or a smooth, extensive mass. The clear, translucent, pearly gray or pale blue sheet resembles icing on a cake and is referred to as the "iced," "sugar coated," or "zuckerguss" spleen. This occurs often in chronic syphilitic hyperplasia but is not confined to that disease. Calcification may be extensive and ossification may occur.

Suppuration in the neighborhood of the spleen such as subdiaphragmatic abscess or that originating in neighboring organs is referred to as parasplenitis.

LYMPH NODES

Introduction.—Since practically all the absorption of substances in solution and the transport of particulate matter in the body is through the lymphatic vessels, the lymph nodes are in direct line of attack by injurious materials. Particulate substances may be retained permanently within the lymph nodes or may pass on into the blood circulation. Substances in solution pass through the lymph nodes and gain access to the general body circulation. The cells and tissues of the lymph nodes react variously to the passage of irritant substances of differing character. The pathological alterations, therefore, are practically always secondary to some condition in the area drained by the lymph node or nodes concerned. Certain other conditions, however, are regarded at present as primary in lymph nodes, because their mode of origin has not been determined. These, however, are infrequent in proportion to the secondary lesions and include such conditions as Hodgkin's disease, lymphoma, lymphosarcoma, Gaucher's disease, etc.

Retrogressive Conditions.—Pigmentation of lymph node is common, particularly in the mediastinum where coal pigment is deposited from the lungs. Similarly, other dusts such as silica, lime, iron, vegetable dusts, etc., also occur. This is seen primarily in the sinuses either free or within endothelial phagocytes but later is found in the pulp cells. It may lead to considerable fibrosis of the nodes. Inflammatory or necrotic lesions of the node, particularly such as occur in tuberculosis, may produce adhesion to and then rupture into surrounding structures. Rupture into a vein may be followed by anthracosis (or siderosis, etc.) of other organs, especially liver and spleen. The pigment of tattooed skin is transported sometimes in considerable quantities to regional lymph nodes. Nodes draining areas of hemorrhage may be pigmented with hemosiderin, either transported as such, or formed by destruction of transported erythrocytes within the node. The pigment of skin in Addison's disease may also be transported to lymph nodes. It is stated also that the implantation of negro skin on white skin leads to pigmentation of regional nodes. Cloudy swelling and fatty degeneration may appear in the lymph nodes, usually as the result of inflammatory lesions of various degrees. These are evident only on microscopic examination and particularly in the endothelial cells of the sinuses. Amyloid infiltration occurs as a part of general amyloidosis but may be seen also in connection with tumor invasion. It occurs along the connective tissues and the walls of capillaries and arterioles. It may be so extensive as to lead to marked atrophy of the adenoid substance. Hyaline degeneration may appear in the blood vessels of the nodes but is more commonly a part of chronic inflammation of the nodes, particularly that due to tuberculosis. It is essentially a connective tissue hyalin due to transformation of bands of connective tissue, and has been referred to as von Recklinghausen's hyalin when connected with tuberculosis of the node. Calcification of the lymph nodes occurs particularly as the result of calcification of tuberculous areas or under other circumstances where necrosis is present. It is sometimes observed in cancerous nodes,

especially where there is a psammomatous cancer. Passive hyperemia is not uncommon, and more especially when there is inflammation present, hemorrhage may be observed. Edema also occurs, more particularly in acutely hyperplastic or inflamed nodes. After puberty, the nodes undergo a gradual regression throughout life and in old age show distinct atrophy. The atrophy is a simple decrease of the cellular element with a relative and sometimes absolute increase of connective tissue. Not infrequently there is a fat substitution of the atrophic areas by an ingrowth through the hilus, a condition likely to be well exemplified in the retroperitoneal nodes of obese individuals.

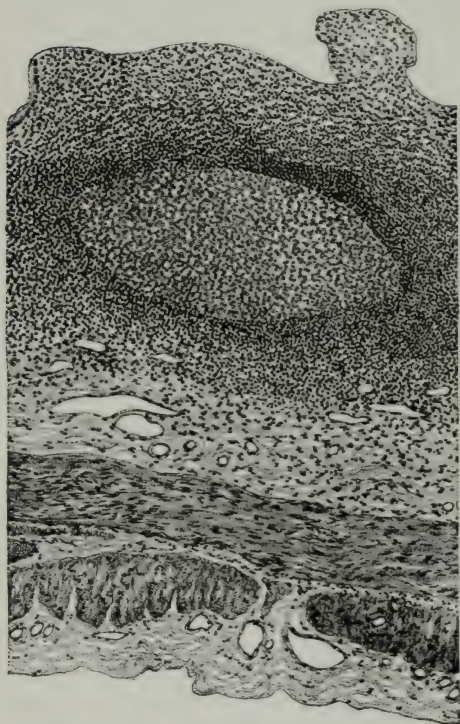


FIG. 232—Acute hyperplasia of intestinal lymph node.

Acute Hyperplasia.—Acute hyperplasia of the lymph nodes, or acute hyperplastic lymphadenitis, occurs under conditions somewhat similar to those observed in the spleen. Although there may be no exudation, nevertheless this type of reaction to irritants is broadly regarded as of inflammatory nature. If the primary lesion be focalized, the affection of the lymph nodes is usually confined to the group which drains the diseased area. Thus, injuries and infections of the lower extremities are likely to be accompanied by acute hyperplasia of the lymph nodes of the groin, and those of the upper extremities affect the epitrochlear and axillary lymph nodes. Lesions of the mouth and throat affect the draining nodes of the neck. The condition may be produced by dissolved irritants, but even when bacteria are present the lesion of the lymph node does not necessarily pass beyond the stage of hyperplasia. If,

however, the organisms be sufficiently virulent and survive the resisting powers of the lymph nodes, abscess formation or acute suppurative lymphadenitis may occur. There is usually a certain degree of lymphangitis but this may be sufficiently mild to escape detection. The node is large, soft, red from hyperemia, and with a tense capsule. It cuts with slight resistance and shows a bulging, pink or red, soft cut surface from which the pulp can easily be scraped. Hemorrhage is also sometimes present. Histologically, the node shows enlargement of the follicles, often with an increase in the size of the germinal centers. These central cells may show mitotic figures and especially in young individuals a certain amount of necrosis, granular or hyaline. The pulp is usually hyperemic and shows increase in the number of endothelial cells which are swollen, sometimes degenerate and often phagocytic for red blood corpuscles, cell debris

and bacteria. As with the spleen, certain types of acute hyperplasia may show special features. Thus, in typhoid fever the phagocytic activity of the endothelial cells is likely to be pronounced. In lesions secondary to suppurative areas there may be a moderate infiltration of polymorphonuclear leucocytes into the nodes. In anthrax a hemorrhagic condition and even considerable necrosis may occur, and the same is true of bubonic plague. In some infections there may be fibrin formation, more marked in the sinuses.

General enlargement of the lymph nodes which can easily be discerned upon examination of superficial nodes is a very common concomitant of many acute infectious diseases, such as scarlatina, measles, diphtheria, varicella, smallpox and others. The enlargement also affects deep nodes and those of the intestinal canal, both Peyer's patches and solitary follicles. In addition there may be more striking enlargement of local areas, as for example those of the neck in cases of diphtheria and scarlatina, those in the abdominal regions in typhoid fever, and those of the inguinal region in cases of lesions of the genital canal. In syphilis the inguinal nodes are enlarged early in the disease but in the secondary stage general enlargement is practically constant. Acute disseminated miliary tuberculosis may also show general lymph node enlargement either with or without miliary tuberculosis of the nodes.

Acute Suppurative Lymphadenitis.

—This is most likely to occur in the nodes which drain areas of suppuration. The node is large, soft, pale yellow or hyperemic, and fluctuant. Upon incision pus is discharged. Histologically, the abscess formation begins with a collection of leucocytes either within the pulp or rarely within the follicles, followed by central necrosis and extension of the leucocyte infiltration until an abscess is formed. This may enlarge so as to involve the capsule with consequent suppuration in neighboring structures. Fistula may be produced by pointing into any of the body surfaces. Staphylococci, streptococci, Ducrey's bacillus of chaneroid and gonococci are most frequently encountered.

Chronic Hyperplastic Lymphadenitis.—This is due to prolonged absorption of low grade irritants by the lymph nodes such as may be observed in infections of low virulence, in carious teeth, catarrhal inflammations, chronic skin lesions, and from tumors in the drained area, etc. Chronic hyperplasia may also follow any of the acute hyperplasias or even be the sequence of acute suppuration, or tumor involvement, and of course is likely to accompany chronic infections. In the state of enlargement the node is large, pale, firm, and has a thickened capsule. It cuts with increased resistance and shows a firm, non-bulging or retracting, pale gray cut surface. Histologically, there is an increase

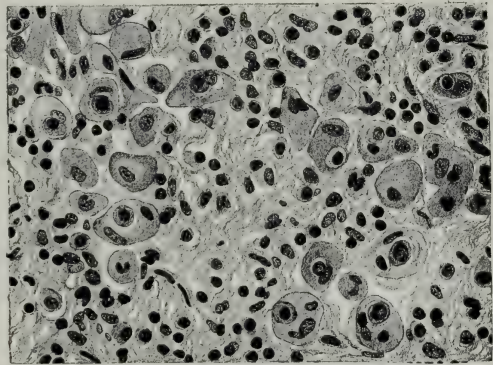


FIG. 233—Acute hyperplasia of lymph node in typhoid fever, showing phagocytic endothelial cells.

in the connective tissue of the capsule and of the node itself, and not uncommonly an enlargement of the follicles and a general increase of lymphoid cells of the pulp. Endothelial hyperplasia of the sinuses may or may not be present. Hyaline degeneration of the connective tissue increases in amount and the adenoid tissue is reduced, and the nodes may then become a small indurated mass. In some instances, fat infiltration proceeds from the hilus of the node. Depending upon the cause and its localization, the chronic lymphadenitis may be confined to a few nodes or a chain of nodes, or as in the case of syphilis, may be generalized throughout the body.

Tuberculosis.—Tuberculosis of lymph nodes is extremely common and can practically always be shown to be secondary to a primary focus in the area drained. There are, however, occasional cases where the primary focus is concealed or has disappeared, under which circumstances the lymph node tuber-

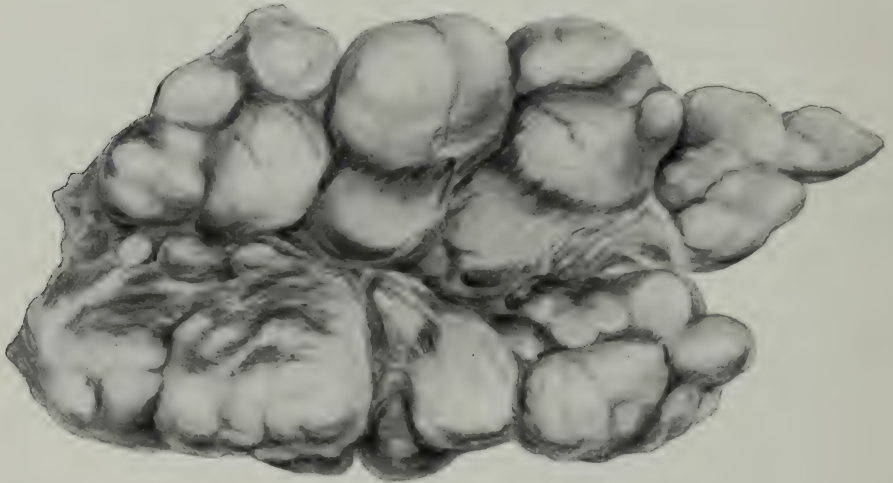


FIG. 234.—Conglomerate tuberculosis of axillary lymph nodes.

culosis appears to be primary. Occasionally, in cases of this sort, a great number of lymph nodes of the body are involved. Affecting the lymph nodes, tuberculosis may appear as a miliary form, as a diffuse cellular hyperplasia, or as caseous conglomerate tuberculosis. In the miliary form of the disease the tubercles are usually multiple and there is an associated acute or chronic hyperplasia of the nodes. The tubercles are frequently characteristic, with necrotic centers, epithelioid and giant cells and a surrounding layer of lymphoid cells. Commonly, however, the tubercles appear simply as masses of endothelial cells surrounded by a thin condensed rim of lymphoid cells. The tubercles are likely to coalesce and form larger masses and when the conglomerate form appears there is usually an acute perilymphadenitis. If the condition persists and the advance be not too rapid, the tubercles may be surrounded by fibroblasts and connective tissue. In diffuse tuberculosis of the lymph nodes there is an irregular cellular hyperplasia consisting of endothelial cells intermingled with lymphoid and plasma cells. Giant cells may also be present. As Warthin

points out, this is presumably due to an infection of low virulence, or it may result from a high degree of local or general resistance. It is likely to be chronic and lead to gradual enlargement of the nodes over a long period of time, subsequently followed by fibrosis and contraction. If the process be focal in the nodes the later stages may show rims of connective tissue around the foci. It is usually limited to a group of nodes but may be generalized throughout the body. Such cases must be differentiated from Hodgkin's disease, lymphosarcoma, Gaucher's disease and other similar conditions. Conglomerate caseous tuberculosis is fairly common. It probably originates as a miliary tuberculosis with rapid coalescence of the miliary tubercles to form a large and caseous mass. The node is large, either soft or firm, depending upon the consistence of the caseous material, and shows a thickened capsule. The condition often extends through the capsules of nodes so as to produce more or less marked coalescence in a chain or group. Coalescence of groups of tuberculous mesenteric nodes is referred to as *tabes mesenterica*. The cut section shows the typical appearance of caseous material. It is usually firm, yellow or yellowish-gray, more or less homogeneous, dry and friable. In some cases the caseous material is soft or semifluid. Histologically, the caseous area is surrounded by a rim of endothelial and lymphoid cells which are often intermingled. There may also be giant cells, and not infrequently daughter tubercles are seen in the surrounding areas. Extension of the caseation into the surrounding tissue may lead to rupture through the skin, through the bronchi or through other neighboring structures, establishing a chronic sinus. This type of tuberculosis is common in the cervical lymph nodes of childhood, in the mediastinal nodes and in the mesenteric and retroperitoneal nodes. Cervical nodes may become infected through lesions of the mouth such as ulceration due to carious teeth, and especially through the tonsils. These foci of entrance may show no or very little tuberculosis in spite of the fact that the cervical nodes may be extensively involved. The mediastinal nodes are usually involved through the lungs where the primary lesions may be absent or so slight as to escape observation. Infection of mesenteric nodes may be due to passage of tubercle bacilli through the intestinal wall, with or without local lesions. It is of interest to note that bovine bacilli play a much more important part in



FIG. 235—Cut surface of caseous conglomerate tuberculosis of lymph nodes, showing necrosis and fusion. Army Medical Museum 30441.

of interest to note that bovine bacilli play a much more important part in

tuberculosis of cervical and mesenteric lymph nodes in childhood than under other circumstances. The portals of entry for the tubercle bacilli may also serve for the establishment of secondary infections and subsequent suppuration.

Syphilis.—In the secondary stages of syphilis the lymph nodes are likely to be enlarged throughout the body, especially evident in the superficial nodes and due to a low grade acute or subacute hyperplastic lymphadenitis. In the later stages this is replaced by a chronic hyperplasia, with subsequent reduction in size of the nodes and increased density with atrophy of the adenoid material. Gumma of the lymph nodes is but rarely observed. A few weeks after the primary infection, the lymph nodes of the groin may become very considerably enlarged to constitute the so-called syphilitic bubo. This is an acute hyperplastic lymphadenitis with a considerable multiplication of fibroblasts. *Spironema pallidum* is present histologically and may be demonstrated experimentally. The condition may regress with a chronic fibrosis of the node or secondary infection may be established and suppuration occur.

Hodgkin's Disease.—This forms fairly large tumor-like masses in the lymph nodes, most commonly in the neck, but affecting other groups such as those of the axilla, thorax, retroperitoneum, mesentery and inguinal region. Gross examination shows that the individual nodes are moderately or considerably enlarged and except in rare instances are discrete and separated from one another by loose connective tissue. Except in the early stages, the nodes are firm, pale or pink in color, with a somewhat thickened capsule. The cut surface may bulge slightly, is usually moist, of pale gray or pink color, and may show minute foci of necrosis. Histologically, the very early stage shows a hyperplasia involving germinal centers of the follicles and the lymphoid tissue of the pulp. The endothelium of the sinuses also shows hyperplasia and there may be some infiltration of polymorphonuclear and eosinophilic leucocytes. Very early, however, the architecture of the nodes is completely obliterated by the marked hyperplasia of connective tissue and cells. The connective tissue hyperplasia is slight in the early stages but progresses throughout the course of the disease, so that in the later stages there may be relatively few other cells remaining. The characteristic cell masses are made up of lymphocytes, plasma cells, endothelial cells, the peculiar mononuclear or multinuclear giant cells of Hodgkin's disease, eosinophiles, and very rarely neutrophilic leucocytes. Small foci of necrosis are not uncommon. As pointed out in the chapter on infectious granulomata, the cause of the condition is not known, the exact nature is not clear, and there is likely to be involvement of other organs and tissues including particularly blood, spleen and liver.

Leucemia.—In the lymphoid form of leucemia general enlargement of the lymph nodes is practically constant. Superficial and deep nodes are involved but large tumor-like masses such as are seen in Hodgkin's disease are not common. The nodes in the acute form are likely to be not only large but show a tense capsule and be of about normal consistence. The cut surface bulges, and is of gray or pinkish-gray color. In the chronic forms the appearance, grossly, is much the same except that in the later stage the nodes are likely to

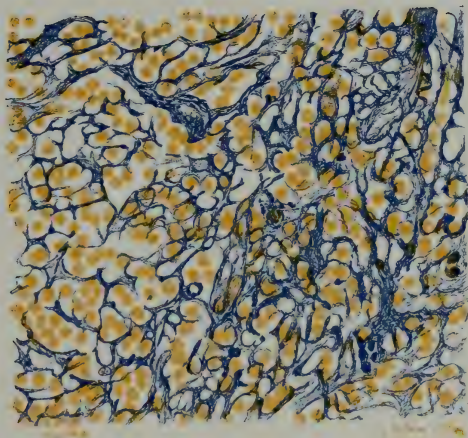


PLATE XVI—Section of lymph node of Hodgkin's disease, specially stained to show connective tissue hyperplasia (Longcope).



be firmer because of fibrous overgrowth. In either form the nodes remain discrete and are not likely to show necrosis. Histologically, the process represents a hyperplasia of lymphoid elements extending out from the follicles. This progresses until the architecture of the node is entirely obliterated by the mass of lymphoid cells. In acute lymphoid leucemia the cells are likely to be somewhat larger than in the chronic forms but often no clear distinction can be made. The reticulum in the early stages is fine and delicate but as time passes, connective tissue overgrowth becomes more and more prominent and in very chronic cases may constitute a large part of the node. Vascularization is present but not likely to be prominent. Lymphoid cells may appear in the capsule as if invasion were occurring. In myeloid leucemia the nodes do not show general enlargement but in occasional cases considerable enlargement is encountered, the nodes being somewhat firm and in the cut surface slightly bulging, moist and of grayish-red color. Microscopically, this is found to be due to a myeloblastic metaplasia of the node or only of parts of it, in which are found the cells characteristic of hyperplastic bone marrow.

The diagnosis of the lymph nodes of lymphatic leucemia is in part determined by the condition of the blood. Rarely, there occurs enlargement of the lymph nodes identical in all respects with that seen in lymphoid leucemias, except that the blood changes are not present. In such cases the condition of the node is referred to as *aleuemic lymphoma*. It is difficult to say that this condition represents an entity separate and distinct from leucemia. It may be an early stage of the process or may represent an intermission, but there are cases on record in which no important blood changes have been encountered at any time, and which must be regarded as certainly not leuemic. In these, lymphoma seems to be an entity, but we do not regard this as firmly established.

Lymphosarcoma.—This is the most important and most frequent primary malignant tumor of the lymph nodes. It usually begins in a group of nodes to which it may remain localized over a long time or from which it may involve many other groups. Favorite points of origin include the lymph nodes of the neck, the adenoid tissues of the throat, particularly the faucial tonsils, the mediastinal lymph nodes, the retroperitoneal lymph nodes and lymphoid tissues of the intestines and of the stomach. Secondary invasion is usually in other lymph nodes either near or remote, but also occurs in organs where lymphoid remnants are likely to be present, such as the liver, the lung and the kidney. Other organs may be involved and we have observed one case in which both adrenals were enormously enlarged by secondary growth. The condition appears to be multicentric in origin in a given chain of nodes, and it is possible that its development in other chains is the result of the operation of the same unknown cause rather than metastasis. Lymphosarcoma shows a distinct tendency to invade through the capsule of the node and into the surrounding tissues, so that within groups of nodes fusion is likely to be marked, and the individual nodes or groups are not freely movable because of the invasion of and adhesion to surrounding parts. Grossly, the nodes are moderately or markedly enlarged, and although individuals of a group may be

clearly made out, there is likely to be a greater or less degree of fusion. Owing to fairly rich vascularization the nodes are likely to be of pink color. The cut surface is soft, bulging, pink in color and shows slight or sometimes extensive necrosis. Histologically, the architecture of the node is completely obliterated. The cellular mass of the tumor may be composed of cells approximately the size of the lymphocyte, the malignant lymphocytoma, or of large cells originating from the reticulum cells of the germinal centers of follicles and pulp cords, the reticulum cell sarcoma or the large round cell lymphosarcoma (Ewing). In both forms the cells may or may not be uniform in size and shape, are round or oval with a moderate amount of cytoplasm and have round or oval, somewhat vesicular nuclei. Multinucleated cells occur in both forms. The principal distinction is in the size of the cells. Mitotic figures are frequent. Vascularization is fairly rich in the form of small vessels and some of these are without independent walls. Reticular connective tissue is present either as a delicate network or, in prolonged cases, as a diffuse fibrous overgrowth. Whether or not a lymphosarcoma may originate in an aleucemic lymphoma is impossible to say. It is to be differentiated from the extremely rare small round cell sarcoma in that the latter is likely to be an alveolated tumor, the cells of which are uniform in size, poorly vascularized and with little or no intervening reticulum other than the walls of the alveoli. The blood may show nothing other than secondary anemia, but in certain cases, more especially those primary in the intestine, there may be a relative or absolute lymphocytosis.

Endothelioma.—This also may involve single groups of nodes such as the cervical or axillary or may be systemic with the involvement of large numbers of lymph nodes. Invasion of the capsule is not so likely to occur as in the lymphosarcoma but in the later stages may be very apparent. Vascularization is less marked in these tumors and the color is likely to be pallid. Necrosis is not uncommon. Ewing finds that this condition is likely to develop upon a preëxisting granulomatous involvement of some sort. Histologically, the condition is characterized by the presence of solid sheets of large round cells, at first in the sinuses of the nodes and later invading more widely. The cytoplasm is rich and may be somewhat vesiculated, the nuclei relatively small and vesicular. The massing of the cells in sheets may give the tumor a somewhat alveolated appearance, but there is not likely to be great fibrous tissue overgrowth or fibrous trabeculae except in later stages. Mitotic figures may be observed. As with lymphosarcoma, secondary growth is more likely to occur in other lymph nodes, but metastatic involvement may be more extensive and appear widespread over the body.

Secondary tumors of the lymph nodes are very common, particularly as metastasis from carcinoma. These may exactly reduplicate the original growth and appear as squamous, adenomatous or simple forms. On the other hand, loss of differentiation may occur so that a fairly well differentiated primary tumor may show carcinoma simplex in the lymph node metastasis. The growth appears first in the sinuses of the nodes, gradually invades, and may even penetrate through the capsule. If resistance be high, considerable con-

nective tissue growth may occur, with such secondary changes as hyalin and calcification. Secondary sarcomas also reduplicate the appearance of the original tumor. These may appear primarily in the lymphoid sinuses, or may be found within the pulp of the nodes because of vascular transmission. Chloroma is especially likely to metastasize to lymph nodes and produce considerable enlargement. The involvement is uniform throughout the nodes and may sometimes invade the capsule. It is characterized grossly by the green tint of the node and microscopically by the myeloid, lymphoid or plasma types of cell.

Parasites.—Those mentioned as occurring in the lymph nodes include the echinococcus, cysticerci and, more particularly in the mesenteric lymph nodes, the trichinella spiralis. The lodgment of filaria sanguinis hominis in the larger lymphatic vessels and also in the nodes is the cause of that chronic form of edema known as elephantiasis.

Hemolymph Nodes.—These are usually embedded in fat near large blood vessels and are found in the prevertebral retroperitoneal region, near renal vessels, about the brim of the pelvis, the root of the mesentery and sometimes in the omentum. They are small, red, mottled or pale nodes, whose color can be seen best by transmitted light. They differ from lymph nodes in that the capsule is thicker and there are blood sinuses instead of lymph sinuses, although the latter may also be present. Little is known of their pathological changes, but Warthin points out that they have an important part in hematopoiesis, especially in blood destruction. In infections of various kinds they show acute hyperplasia, well marked in the sinuses where endothelial phagocytosis of erythrocytes is prominent. Hemosiderosis may be marked. In secondary anemias the nodes may show marked myeloid metaplasia, but in pernicious anemia blood destruction is the most conspicuous feature. The leucemias show marked lymphoid or myeloid metaplasias. Banti's disease shows marked hyperplasia, blood destruction and increase in the number of hemolymph nodes. Symmers reports a hemangiolymphoma of hemal nodes, which may give rise to local or selective subperiosteal metastases.

BONE MARROW

Retrogressive Processes.—The bone marrow may undergo a marked hyperplasia in infancy and childhood as a result of severe anemias. Cells of the bone marrow may show cloudy swelling and fatty degeneration when inflammation occurs. Probably the most significant change in the bone marrow is the so-called gelatinous degeneration. This may be acute or chronic and is the sequence of prolonged exhausting diseases such as chronic tuberculosis, malignant tumors, and chronic nephritis; of poisoning by metals such as lead, mercury, and arsenic; of inanition; and sometimes appears as the result of advanced senility. It may also represent exhaustion following such hyperplasias of bone marrow as appear in the anemias and leucemias and is well seen in aplastic anemia. Grossly, the marrow has a yellow or pinkish-yellow color, is somewhat reduced in volume, and shows a gelatinous, semitranslucent

appearance. Histologically, there is reduction in the blood forming constituents and in the fat, the connective tissue cells becoming transformed into stellate and spindle cells with a matrix between, which closely resembles mucoid. Toxic agents such as benzol and mustard gas (Krumbhaar) may produce much depression of bone marrow. Simple atrophy of the marrow may be due to senility, to exhausting diseases, to the advancement of osteosclerosis and to exposure to x-rays. With the simple atrophy there is usually an accompanying fibrosis. Anemias of all varieties may be accompanied by hemosiderin pigmentation of the bone marrow. Malarial pigmentation may be prominent. Schridde reports anthracosis, and also pigmentation of the marrow in the neighborhood of secondary nodules of melanosaarcoma. Small areas of necrosis,

which may be visible to the naked eye, may appear in the bone marrow as the result of certain infectious diseases such as typhoid fever, pneumonia, smallpox, plague, septicemia, etc.

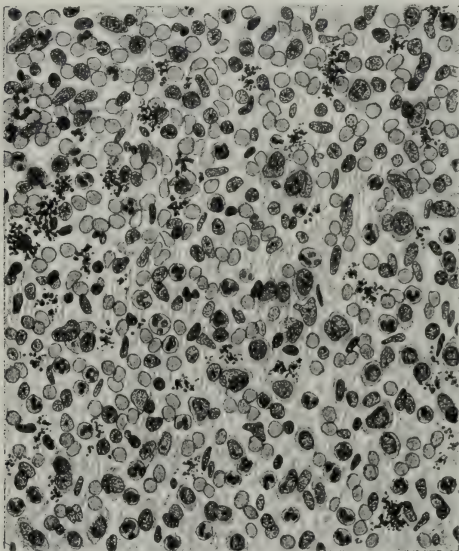


FIG. 236—Malarial pigmentation and hyperplasia of bone marrow.

Hyperplasia.—The bone marrow is in such intimate connection with the circulating poisons of various diseases, is so accessible to bacterial infection, and plays such an important part in the provision of blood elements (leucocytes) to combat infection in any part of the body, that it is to be expected that hyperplastic changes often occur. Hyperplasias may not only accompany conditions of this sort, but occur as chronic or prolonged hyperplasia in anemias and leucemias. Although with the first demand for hyperplasia the reaction is likely to

take place in all the elements of the bone marrow, nevertheless, as time goes on, one or more groups of elements may predominate and the hyperplasia may therefore be erythroblastic, leucoblastic or in some cases lymphoblastic. Further subdivisions are possible because of predominance of particular types of cells. Thus, there may be a normoblastic or a megaloblastic type of erythroblastic hyperplasia. Similarly, the leucoblastic hyperplasia may show predominance of the neutrophilic, eosinophilic, basophilic or myeloblastic type. The erythroblastic hyperplasia may be confined to those situations in which red marrow is normally present or may be so extensive as to involve marrow which is normally fatty, thus appearing in the shafts of long bones. The milder forms of hyperplasia occur in secondary anemias, but both in these forms when severe, and in primary anemias, erythroblastic hyperplasia may be very pronounced. Hematologically, the megaloblastic hyperplasia should be more prominent in pernicious anemia, but this is difficult



PLATE XVII—Drawing showing on the left, hyperplasia of bone marrow in pernicious anemia and on the right, gelatinous marrow as a stage of exhaustion following hyperplasia.

to demonstrate in the histology of the marrow. The neutrophilic leucoblastic hyperplasias are especially common in connection with leucocytosis. It is only when the primary infection is prolonged and severe that hyperplasia extends into the shaft of the long bones. A preponderance of the non-granular myeloblasts may be observed sometimes in cases of prolonged leucocytosis, but is more characteristically observed in cases of leucemia. Eosinophilic hyperplasia is often observed in trichinosis. Lymphoblastic hyperplasia may be observed in lymphatic leucemia and in status lymphaticus. These are described in detail by Dickson and have been referred to in the previous discussion of diseases of the blood. Considering the bone marrow as a whole, these changes represent hypertrophy because there is associated increase in the fundamental activity of the bone marrow, but in considering cell groups there is no reason for believing that the functional capacity of individual cells is increased, and it therefore seems desirable to refer to these changes as hyperplasia rather than hypertrophy. The hyperplasias of the anemias and leucemias are essentially chronic in character except when those diseases run acute courses. In addition, however, the bone marrow may show chronic hyperplasia principally in the form of an overgrowth of connective tissue, associated sometimes with infiltrations of lymphocytes and plasma cells. Such conditions may accompany certain chronic diseases such as chronic pulmonary tuberculosis, chronic nephritis, cirrhosis of the liver, etc.

Inflammation.—Infections in the body may lead to the hyperplasias mentioned above or may directly involve the bone marrow in inflammatory processes. Thus, in staphylococcus septicemias small abscesses, sometimes visible to the naked eye, are found in the bone marrow. This is of little functional significance since other parts of the marrow may serve all necessary purposes. Healing results in the formation of small scars. Such diseases as typhoid fever, pneumonia, smallpox and plague are likely to show in the bone marrow small foci of necrosis surrounded by hyperemia, edema and fairly rich fibrin formation. In the immediate neighborhood, phagocytosis of corpuscles by endothelial cells may be prominent and after the lesion has healed, hemosiderin pigmentation is likely to be observed. In typhoid fever there may be little or no necrosis and the lesion be represented simply by focal accumulation of endothelial cells, phagocytic for bacteria and cell debris similar to the lesions observed in the liver and spleen (Mallory).

Abscess formation in the marrow, as indicated above, is of little direct significance so far as function of the marrow is concerned. Nevertheless, extension is likely to occur involving the bony substance leading thus to an osteomyelitis. Although other organisms occur, the staphylococcus is most frequently associated with this condition.

Granulomata.—Tuberculosis of the bone marrow commonly accompanies an acute disseminated miliary tuberculosis. Histologically, the miliary tubercles have the usual form. The marginal lymphocyte zone may be somewhat richer in plasma cells than is ordinarily the case in other tissues. The

most serious involvement by tuberculosis is that which includes not only the marrow but also the bone. This is likely to occur in the ends of long bones, more especially in childhood, and also in spongy bones such as the bodies of the vertebræ. It is an important cause of amyloid disease.

Only rarely do gummata appear in the bone marrow. In Warthin's cases of late syphilis, "premature and excessive osteoporosis of the bone and fatty atrophy of the marrow characterize the majority of cases. In a small number of cases, the lymphoid marrow was found to be increased."

In Hodgkin's disease the bone marrow not infrequently shows nodular deposits of essentially the same character and cell composition as seen in lymph nodes and spleen.

Tumors.—It is only rarely that primary benign tumors occur in the bone marrow. Occasional cases of hemangioma, chondroma and fibroma have been reported. The malignant tumors include particularly the *multiple myeloma*. This is likely to attack primarily the active red marrow and appears particu-

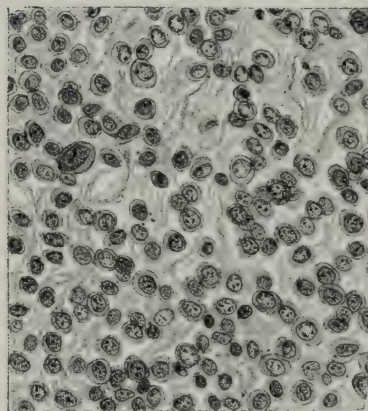


FIG. 237.—Multiple myeloma with cells of myelocyte type.

larly in the ribs and sternum. Nevertheless, the vertebræ, skull, femur, pelvis, and humerus are also involved, in the order of frequency named. Grossly, the tumors are found to be nodules of variable size, sometimes soft, sometimes firm; they may be somewhat translucent or opaque and are gray or red according to vascularization. Various forms are described histologically. The essential cells may be plasma cells (Christian), myeloblasts or erythroblasts. The identity of these two latter forms of cells is not clearly established and Ewing suggests that they may all be various degrees of anaplasia of some fundamental cell type. The cells are supported

on a very delicate reticulum. Both grossly and histologically, invasion and destruction of the surrounding bone are seen and the tumor may indeed perforate through the bone. As the disease progresses the bony involvement is likely to become more extensive. Distant metastasis is not common (Symmers) but may occur in liver, spleen, kidney, lung and other viscera. The lymph nodes are not especially susceptible to metastasis. The disease is more common in males in the fourth and fifth decades of life, is accompanied by progressive cachexia, and often shows Bence-Jones albumose in the urine. Occasionally a similar type of tumor is found as a single mass in bone, sometimes with metastasis to distant parts. This is referred to as the myelosarcoma. We have observed one case in which the tumor was primary in the lower end of the femur and metastasis occurred in the brain. The blood in multiple myeloma usually shows only secondary anemia, but there may be an increase in myelocytes in the circulating blood and in rare cases even supposed plasma cells.

Endothelioma.—This tumor of bone may occur in a single large mass or as multiple masses in the bone ends and shafts. In the latter case it may clinically resemble the multiple myeloma. Ewing calls special attention to the susceptibility of this type of tumor to x-ray treatment, although cures are not often permanent. Histologically, the tumor is likely to combine invasion of bone marrow and bony substance. It is made up of sheets of cells sometimes in an alveolated arrangement, sometimes poorly and sometimes well vascularized and with relatively little reticulum. The cells in some tumors show solid cytoplasm and in others the cytoplasm is somewhat vesicular. Metastases to other parts are distinctly unusual. As with the myeloma and chloroma, the endothelioma shows no tendency to bone formation itself. Cases occur in which it appears that endotheliomatous and hemangiomatous forms represent phases of multiple myeloma (Wells).

Chloroma.—Closely related to the multiple myeloma is the tumor called chloroma or sometimes chloromyeloma. This invades bone from the bone marrow in much the same manner as does myeloma, but more commonly involves the lymph nodes in addition to metastasis in other organs. It is characterized grossly by a pale green color. Microscopically, the tumor is made up of cells with granular cytoplasm, either neutrophilic or eosinophilic and sometimes mixtures with one or the other form predominating. Basophilic cells do not occur. Alterations of the blood are very common, particularly in the form of a mild anemia or moderate increase of the cells of the myelocyte series, or both. Considering the possibility of changes in the blood in the chloroma and the myeloma a certain resemblance to myeloid leucemia is observed. The latter, however, shows little or no invasion of bony substance and does not produce large metastases in organs in the same way as these clearly demonstrable tumors.

Secondary Tumors.—Any type of malignant tumor may metastasize into the marrow of bones. Most common, however, is carcinoma and especially those forms originating in the prostate, thyroid and breast. This does not exclude the possibility of other cancers producing metastasis in the bone and we have observed it in several cases of carcinoma of the stomach. Such metastasis may be widespread throughout the skeleton, but is most frequently observed in the long bones, particularly the femurs and also in the spongy bones, particularly the vertebræ. The neighboring bone marrow may show a distinct hyperplasia. The tumor, however, enlarges and produces in the bone sometimes an excessive new formation of bone, but more often a destruction of the bone which thereby becomes susceptible to what are called pathological fractures.

THE RETICULO-ENDOTHELIAL SYSTEM

Since the introduction of the intravital staining methods of Goldman and the extensive studies of Aschoff, Kiyono, Maximow, Downey, Foot and many others, an extensive literature on the subject has grown and the term reticulo-endothelial system has gained widespread adoption. This is variously inclusive, but for the sake of simplicity the reticulo-endothelial system may be said to include the mesoblastic mononuclear cells present in many organs of the

body capable of phagocytosis of foreign particles, cells and cell fragments and bacteria, serving as points of storage for certain materials, acting in some capacity in the metabolism of the body and perhaps, as indicated by Gay, exercising a function in local immunity. In this group of cells are the fixed reticular cells or resting wandering cells, clasmatoocytes, pyrrhol cells, macrophages, adventitia cells, endothelial leucocytes, histiocytes, Kupffer cells, splenocytes and others. There is discussion as to whether or not the endothelial cells of blood and lymph channels and the monocytes of the blood are to be regarded as a part of the system. The studies of Mallory and others indicate that wandering cells of the tissues and monocytes of the blood may be derived from vascular endothelium. Maximow's scheme of cells of this order indicates an interrelationship prominent in the embryo and present in postembryonal life. For the present it seems useful to take the widely inclusive view. The part the system plays in the hematopoietic system is not finally settled. Maximow describes the hemocytoblast from which may be derived blood cells. In destruction of blood cells, more especially erythrocytes, it seems probable that earlier deterioration occurs in the circulation, that the reticulo-endothelial cells, particularly in liver, spleen, lymph nodes and bone marrow ingest and destroy cells, and that further changes of the soluble products take place elsewhere. It is well known that in certain acute infections such as acute glandular fever, certain cases of Vincent's angina and tuberculosis (Landon), the blood may show a striking increase in large mononuclear cells, mononucleosis, but that this is a result of stimulation of the reticulo-endothelial system is still open to question.

Under various circumstances the storage of fats and lipoids in the reticulo-endothelial system may reach pathological proportions. Bloom has distinguished the clinical and pathological features of Gaucher's disease and Niemann's disease, referred to above; the first, an anomaly of lipid metabolism with deposit or storage of cerebrosids in reticulo-endothelial cells of the hematopoietic system; the second, an anomaly of lipid metabolism with storage of phosphatids not only in the hematopoietic system but also elsewhere. The studies of Anitschkow and others show that feeding excess of cholesterol results in extensive storage of cholesterol, more complex lipoids, and perhaps fat, in reticulo-endothelial cells in various parts of the body. Reports by Oppenheimer and Fishberg and by Warren and Root, show that in the lipemia of diabetes and icterus, storage in reticulo-endothelial cells especially of the spleen and also liver, aorta and endocardium may be pronounced. The material stored includes cholesterol and its esters, phosphatids and neutral fat. The yellow color of xanthomatous patches and tumors is due to storage of lipoids in certain groups of cells, many of which are reticulo-endothelial in nature.

These instances are probably to be regarded as due to abnormalities of metabolism with resultant storage of incomplete products. Cells of this order have much to do with removal and destruction of substances produced by injury to tissues, as indicated in the chapter on inflammation. They further serve as storage places for inert particulate matter, such as pigments, which cannot be broken down and removed from the body.

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CHAPTER XV

THE RESPIRATORY SYSTEM

NOSE.
LARYNX AND TRACHEA.
BRONCHI.
LUNGS.
PLEURA.

THE NOSE

Congenital Anomalies.—The nose may be markedly deformed, cleft or absent, in cases of marked facial or cranial malformation. Stenosis or atresia of the posterior nares, absence of septum, absence or deformity of one or more turbinal processes, and deviation of septum occur. Clefts of the floor of the nose and anterior nares occur with cleft palate and harelip.

Circulatory Disturbances.—Active hyperemia, particularly in the vascular turbinal processes, occurs as the result of irritants of various kinds including gaseous, particulate and organismal. This may or may not be the preliminary stage of an inflammation. Passive hyperemia occurs in connection with chronic heart and lung disease as well as local interferences with venous drainage. Hemorrhage from the nose, or epistaxis, may be due to trauma, to active or passive hyperemia, to acute or chronic inflammation, to tumors, particularly the nasal polyp, to anemias and leucemias and to such hemorrhagic disease as scurvy and hemophilia; it may be a prodromal sign of or accompany certain acute infectious diseases. Ulcers of various kinds including those of syphilis, tuberculosis, etc., may lead to hemorrhage. In extremely rare cases typhoid ulcers may appear in the nose and lead to hemorrhage. Hemorrhage may also represent vicarious menstruation. It is only in case of chronic ulcers, tumors and the hemorrhagic diseases that epistaxis is likely to be serious.

Acute inflammations may be catarrhal, purulent, ulcerative and fibrinous. Acute inflammations of the nose may be accompanied by similar inflammations of adjacent mucous membranes, such as those of the accessory sinuses, conjunctiva, and middle ear. The most frequent example is the common cold. Whether the common cold represents an inflammation due to organisms constantly present in the nose, incited to activity by other conditions such as hyperemia from exposure to cold, or whether it be due to a special organism is not definitely settled. The experiments of Kruse, of Foster, and of Olitsky and McCartney, however, would indicate that a filterable virus is the exciting cause. Mudd and his colleagues demonstrate that exposure of the body surface to cold leads to reflex vasoconstriction and ischemia of nose and pharynx, which possibly reduces local resistance. The first change in the mucous membrane is hyperemia, followed rapidly by pouring out of a considerable amount of serous or seromucous secretion. This subsequently becomes yellow and thick because of increased content of leucocytes and mucin. In the stage of serous exudation, the mucosa shows cloudy swelling of the epithelium and increase in mucoid material in the glandular cells, together with an infiltration of lymphoid cells into the tunica propria. Subsequently the degenerative change becomes more marked,

desquamation of surface epithelium occurs, and the membrane becomes infiltrated with polymorphonuclear leucocytes. Local inflammations, with or without involvement of adjacent structures, may also be due to inhalation of irritant gases, to inhalation of large quantities of dust, and to inhalation of protein dust to which the individual is hypersusceptible, as exemplified by hay fever, etc.

Acute purulent rhinitis may be secondary to an acute catarrhal rhinitis, because of the activity of the pyogenic bacteria. It may also be primarily due to pyogenic bacteria, gonococci, or the presence in the nose of foreign bodies. It may occur in measles, scarlatina, smallpox, and other acute infectious diseases. It is likely to be accompanied by purulent infection of the accessory air sacs. It may rarely lead directly to meningitis, or more commonly, indirectly through the involvement of the accessory air sacs.

The most important cause of fibrinous rhinitis is the diphtheria bacillus. This may produce an acute diphtheritic rhinitis which, because of the large area of absorption provided, may be accompanied by serious toxic symptoms, or may produce a chronic diphtheritic rhinitis. The latter may apparently produce no symptoms other than the viscid discharge, but serves as a focus for dissemination of diphtheria bacilli to other individuals. Fibrinous inflammations may also be caused by other organisms such as the streptococcus and pneumococcus.

Chronic inflammations may be of hypertrophic or atrophic variety. In the former, the mucosa is thickened either by fibrous overgrowth or lymphoid cell infiltration, or both, in the tunica propria. It may be diffuse throughout the nose or especially prominent in the turbinal bodies. It is not uncommonly associated with polyp formation. The discharge from the nose may be serous, mucous or purulent. The chronic atrophic rhinitis may be primary or may follow the hypertrophic form. There is considerable atrophy of the surface epithelium, often with loss of cilia and further metaplasia to form flat cells, atrophy of the glandular epithelium and the formation of a dense connective tissue in the tunica propria. The contraction of the connective tissue may lead to considerable shrinkage of the turbinal bodies. The discharge from the nose is usually thin and serous in character. *Ozena* or fetid chronic atrophic rhinitis, is a form of the disease characterized by foul odor and the formation of crusts. It occurs especially in wide faced individuals. The mucosa and glands are atrophic and the surface epithelium shows metaplasia to a stratified squamous form. Believed by some to be due to a special organism, the so-called bacillus ozenæ, this organism is now considered to be Friedlander's pneumobacillus and the odor probably due to stagnation and putrefaction of secretions. The glands are inactive and secretions are not removed by flow, by activity of cilia or by an adequate intensity of air current. Syphilis is believed by some to be the cause but this is not constantly proven; the condition, however, is common in congenital syphilis.

Granulomata.—Tuberculosis of the nose is not common but may occur in two main forms, the proliferative or the ulcerative. The latter is likely to occur in patients who are otherwise tuberculous, and may complicate tuberculosis of the pharynx and of the larynx. The proliferative type may extend from the

skin through the anterior nares, or may be apparently primary. Tuberculosis of the nose is most common in the cartilaginous portion of the septum, but may also appear in the turbinal processes and even involve the bony substance. It is usually unilateral and produces no important symptoms other than obstruction to the nose and a slight secretion. The proliferative form is characterized by multiple miliary tubercles restricted to a small area, or may appear as a large tuberculoma. Histologically, the tubercles show a rich lymphoid infiltration, a moderate number of epithelioid and giant cells and relatively little disposition to caseation. The demonstration of tubercle bacilli or the infection of animals by the material, is essential to the positive diagnosis of tuberculosis, for syphilis presents confusing gross and histological pictures and is much more common in the nose than is tuberculosis. Rarely, tuberculosis of the nose of the proliferative variety, and sometimes of the ulcerative variety, may produce the symptoms and signs of ozena.

Syphilitic involvement of the nose is common. Congenital syphilis may give rise to a chronic atrophic rhinitis with foul smelling discharge, a syphilitic ozena. There also occurs a form in which primarily there is papule formation, particularly upon the septum, followed by ulceration. The ulcers may perforate the septum and destroy a large portion of cartilaginous and bony substance. This is the usual cause of the "saddle nose" of congenital syphilis. Although chancre may appear upon the exterior of the nose it is extremely rare in the interior. Secondary lesions may involve the nose. Of greatest importance, however, is gumma within the nose which involves particularly the septum and originates usually in the periosteum or perichondrium. The breaking down of the gumma leads to ulceration which often perforates the septum. The process may give rise to pain, to foul discharge, to obstruction and to hemorrhage which may be severe. Extensive ulceration may produce the "saddle nose" of acquired syphilis.

Glanders may affect the human nose in the same manner as that of the horse. It produces a nodular growth which tends to break down and form ulcers with a yellow necrotic base. These may invade cartilage and bone with perforation of the septum. From the profuse secretion the glanders bacillus can be isolated. The mass is grossly granulomatous in character, and histologically is made up of lymphoid cells, leucocytes, and endothelial cells with distorted cytoplasm and nuclei, as described in the chapter on infectious granulomata. Central necrosis occurs and when ulceration follows, the picture of leucocyte infiltration becomes more pronounced.

Leprosy is likely to be primary in the nose, where it forms at first a small lepra nodule which may subsequently become ulcerated. In some cases ulceration may be pronounced and lead to perforation of the septum. Acid fast bacilli are found in smears from the nose and the histological picture shows a low grade chronic granuloma with the typical lepra cells.

Rhinoscleroma originates usually in the posterior part of the nose and leads to a dense cellular infiltration which may extend anteriorly, but more commonly invades the pharynx and the posterior part of the mouth. The bacillus of rhinoscleroma may be recovered from discharges or identified in the material.

Histologically, the granuloma is fairly characteristic, being made up of lymphoid and plasma cells in the midst of which are numerous Mikulicz cells.

Tumors.—The most common tumor or tumor-like process is the nasal polyp, which may be sessile or pedunculated. The sessile form may be merely a local manifestation of a chronic hypertrophic rhinitis, or may be adenomatous in character due to proliferation of the mucous glands. The pedunculated form may be adenomatous, may rarely be a polypoid myxoma, but most commonly is the edematous fibroma. The polypoid tumors are usually attached to the lateral walls near the opening into the antrum of Highmore. The adenomatous varieties are probably true tumors. The myxomatous and edematous fibromata have been discussed in the chapter on tumors, and it was there pointed out that some doubt exists as to whether these represent true tumor formation or growth of connective tissue incident to chronic inflammation. The movement of air in the nasal sinuses is such that the pedicle may undergo twisting, with subsequent edema of the connective tissue. Mucoid degeneration of the connective tissue may occur under a variety of circumstances. Other benign tumors of the nose include chondroma, osteofibroma, osteoma, and dermoid cysts. These, however, are comparatively rare.

The sarcomas include particularly the round cell sarcoma, the spindle cell sarcoma, and angiosarcoma. The round cell sarcoma is the most common and is likely to begin in the posterior part of the nose or in the soft palate, rapidly extending posteriorly and anteriorly. Carcinoma is not common, but when it occurs is usually a cylindrical cell carcinoma simplex or an adenocarcinoma. Squamous epithelioma may arise from metaplasia of the cylindrical epithelium or may result from extension from the anterior nares or mouth. A very rare tumor is that arising from the Schneiderian membrane, involving the nose and metastasizing to the lymph nodes of the neck. Secondary tumors result from extension of neighboring tumors, as those of the orbit, or are rarely true metastases.

Accessory Air Sacs.—These are usually involved together with the nose in acute and chronic inflammations. Although sphenoid and ethmoid cells may be attacked, the antra of Highmore and the frontal sinuses are more frequently involved. Usually they drain well and no further trouble results. If drainage be poor the infected secretion remains and may lead to hydrops (seromucous secretion) or to empyema, both of which are commoner in the antra than the frontal sinuses. Of considerable importance in causing antrum infection is infection of upper teeth and alveolar processes. Tumors are much the same as in the nose, the carcinoma being not uncommon.

Of great importance is the fact that inflammations of the nasopharynx may involve the Eustachian tube and extend into the middle ear and mastoid air sacs.

Leucemic infiltrates may occur in the lymphoid tissues of the nasopharynx.

LARYNX AND TRACHEA

Congenital Malformations.—Various cartilages as well as the entire larynx may be hypoplastic or absent. There may be atresia of the larynx and also membranous bands leading to stenosis. Outpouching of the ventricle of the

larynx may be apparent upon external examination of the neck. The trachea may be the seat of stenosis or atresia, the latter occurring usually at the upper end and often with an esophageal fistula. Occasionally, there are two main bronchi to the right lung. Failure of complete obliteration of the branchial clefts may produce external fistula, branchiogenic cysts or fistulæ between the skin surface and either pharynx or trachea.

Circulatory Disturbances.—Passive hyperemia due to general or local causes is of particular importance in producing chronic catarrhal inflammation. Dilated veins may rupture and produce hemorrhage. Edema of the larynx may be due to passive hyperemia, to local irritation or inflammation. It produces difficulty of respiration and may lead to death from asphyxia. It is called edema of the glottis, incorrectly because the vocal cords are not readily susceptible to edema. The process is found in the lower surface of the epiglottis, the false vocal cords and the tissues over the upper margins of the laryngeal cartilages. The submucous connective tissue is especially involved and the affected areas are swollen, soft, doughy and either pale or red, depending on whether or not inflammation is present.

Inflammations.—The causes of acute catarrhal inflammation are essentially the same for the larynx and trachea as for the nose, and are often secondary to catarrhs of the nose and pharynx. The process accompanies numerous acute infectious diseases and is prominent in the trachea in pertussis, in which condition histological examination may show bacteria in the cilia, morphologically identical with the bacillus of Gengou. Acute catarrh of the larynx may also be due to prolonged and strenuous use of the vocal organs. The acute catarrhs of the larynx produce hoarseness or aphonia. The gross and histological pictures are characteristic of acute catarrhal inflammation. Chronic catarrhs are much more likely to be hypertrophic than atrophic.

Acute fibrinous inflammation of the larynx is usually diphtheritic, usually secondary to diphtheria of the fauces or nose but occasionally primary. Similar inflammations may be due to measles, typhoid fever and other infections. It produces marked difficulty in respiration and even asphyxial death. The fibrinous pseudomembrane covers false and true vocal cords, extends down into the larynx and not infrequently also into the trachea and bronchi. It is



FIG. 238.—Erosions and inflammation of trachea and bronchi due to "mustard gas" inhalation. Army Medical Museum 2792.

usually more firmly adherent in the larynx than in the trachea. It is gray or yellow, smooth or slightly roughened, fairly dense but friable. Histologically, it is made up of a fibrin net extending as far down as the basement membrane and enmeshing leucocytes, lymphocytes, desquamated and necrotic epithelium and various bacteria including the diphtheria bacillus. True croup, due to fibrinous laryngitis, must be distinguished from spasmodic croup, occurring in children in paroxysms of relatively short duration and believed to be due to spasmodic stenosis of the glottis.

Acute purulent laryngitis is usually due to ulceration, such as may accompany tuberculosis, syphilis, typhoid fever, to trauma or to extension from

FIG. 239



FIG. 240



FIG. 239—Syphilitic ulcer of larynx involving vocal cords.

FIG. 240—Ulcerating gummata of larynx and upper part of trachea.

neighboring suppurations. It may be limited to the mucous tissues or be complicated by suppurative perichondritis.

Infectious Granulomata.—Tuberculosis of the larynx is practically always secondary to pulmonary tuberculosis, although rare primary cases are described. The disease may involve the larynx as multiple, small, superficial ulcers, most frequent in the lower part of the epiglottis or as deeper ulcers of the larynx itself, especially about the posterior superior part of the organ. In other cases they are larger, solitary or few in number, deep, with necrotic or caseous base, and irregular, somewhat undermined margins; miliary tubercles may be seen in the base or near the margins. Hoarseness or aphonia are caused either by ulceration of the vocal cords or catarrhal inflammation secondary to

the ulcers. Deep penetration may produce a tuberculous perichondritis. Occasionally, multiple small tubercles or a tuberculous granulation tissue may produce fairly large nodules, originating in the deeper connective tissue and projecting into the lumen of the larynx. It is believed that most cases of tuberculosis of the larynx are due to direct surface infection from pulmonary discharges, but lymphatic or blood transmission cannot be positively excluded.

Multiple miliary tubercles are not rare in the trachea, usually associated with a chronic catarrhal inflammation. Superficial or deep ulcers also occur.

In the secondary stages of syphilis the larynx may be affected either by papules or superficial ulcers similar to those observed in the mucous membranes elsewhere. These usually heal without leaving subsequent scarring of any significance. In late syphilis the lesion may be either a diffuse submucous inflammation of gummatous character, or single, and sometimes multiple nodular gumma, usually beginning within the deeper connective tissue. The gummata are usually small and flat because of necrosis and ulceration, but may project into the larynx sufficiently to produce obstruction. The gummatous ulcers are moderately deep, usually with sharp indurated margins, although in some cases, particularly when secondary infection occurs, the margins may become ragged and undermined. Syphilitic lesions are usually in the upper part of the larynx, not infrequently involving also the base of the epiglottis, but the lower part of the larynx may also be attacked. The vocal cords may be the seat simply of a secondary inflammation or may be in part, or entirely, destroyed by the ulcerative process. Hemorrhage is usually slight but may be severe and even fatal. The deeper ulcers may extend into the cartilage and sometimes into the surrounding tissues of the larynx. Healing of the process, either spontaneously or under treatment, may lead to serious contraction of the scar so as to distort the larynx, or if the process extend into the surrounding tissue may lead to displacement of the larynx. Islands of epithelium between scarred areas may proliferate to form polypoid outgrowths.

Syphilis may involve the trachea in much the same fashion as the larynx and there is sometimes an extension from the larynx. Cicatrization may lead to distortion of the tube.

Leprosy may produce nodular and ulcerative lesions in the larynx and the scar formed after healing may constrict or distort the organ. Glanders, rhinoscleroma, and actinomycosis occasionally involve the larynx.

Tumors.—The commonest tumor is the squamous papilloma which usually originates near or in the anterior commissure of the vocal cords. It may be either single or multiple, either sessile or pedunculated. It constitutes a small, red, moderately firm mass with the usual mulberry-like surface. Histologically, the supporting connective tissue may be either in broad or in very delicate bands, usually fairly well vascularized and covered with stratified squamous epithelium. The design of the papillæ may be so intricate that pearl formation is observed. If placed in fixative promptly, mitotic figures may be seen. The benign growth, however, shows no invasion of the papillary supporting framework or of the underlying laryngeal tissue. It is especially common in singers

and others who use the voice a great deal and frequently originates upon a basis of chronic inflammation. It tends to recur after excision. Polypoid tumors are also fairly common, and may have as a basis a fibroma or a chronic inflammatory type of connective tissue or an adenomatous proliferation of mucous glands. They are covered by stratified squamous epithelium when originating in the false or true vocal cords, or by columnar epithelium in those parts of the larynx where columnar epithelium occurs normally. The epithelial covering usually shows a fairly straight line of basement membrane. Amyloid infiltration sometimes occurs as an isolated process in the larynx, where it may diffusely involve the connective tissue under the mucous membrane or may occur in a nodular, tumor-like form.

Carcinoma of the larynx may originate directly from the surface, from glandular epithelium, or be a malignant change in a squamous papilloma. It is often a projecting nodular ulcerated mass, or may be almost entirely an eroding tumor. The vocal cords are likely to be primarily involved when the process is derived from a squamous papilloma. The projecting forms may give rise to serious obstruction of the larynx whereas the ulcerative forms may produce principally hoarseness, aphonia and cough. Histologically, the picture is fairly characteristic although sometimes the connective tissue may be very dense and produce a scirrhus type of squamous epithelioma. Although combination with tuberculosis and syphilis is possible, it is extremely unusual, and in one of our cases foreign body giant cell formation about the cancer pearls was confused with a granuloma. Metastasis is late and usually involves only the cervical lymph nodes. Submaxillary nodes may be involved and in some cases wide dissemination occurs. Cylindrical cell cancer originating in the surface and glandular epithelium is extremely rare. When sarcoma occurs, which is also extremely rare, it is usually a spindle cell sarcoma which may be of nodular form. Various forms of small round cell sarcoma are also reported. It is probable that many of the latter are really lymphosarcomata originating in preëxisting lymphoid tissue of the larynx.

Tumors of the trachea are very uncommon and among the benign forms there are included ecchondrosis of the tracheal rings, ecchondroma of the submucous tissue, osteoma probably originating upon the same basis. Of the malignant tumors which are also extremely rare, carcinoma is most frequent (Broman), appearing usually as the squamous epithelioma, probably originating in islands of squamous epithelium either of congenital origin or as the result of metaplasia following injury. Secondary tumors sometimes occur but are decidedly unusual. In our experience the most common secondary invasion is extension of cancer of the esophagus into the trachea or bronchi.

Foreign bodies include particles of food which gain entrance to the larynx, more especially in individuals with paralysis of throat muscles and in the insane, or due to carelessness on the part of children. Fragments of tumors of the tongue and of the larynx itself may produce obstruction. Very rarely calculi are observed in the ventricles, forming in accumulated secretion. The muscular tissue of the larynx may be invaded by trichinella spiralis.

BRONCHI

Acute Inflammations.—Acute catarrhal bronchitis is due to essentially the same causes as those given for acute rhinitis and acute laryngitis. The mucous membrane is thick, velvety, red and obscures the underlying muscle markings. The exudate upon the surface may be thin and serous, seromucous, or mucopurulent, depending upon the severity and duration of the disease. Except in infants, children and senile individuals, it usually runs a limited course and leads to recovery. The same is true of the bronchitis of typhoid fever. When affecting the extremes of life, or complicating such diseases as measles or pertussis, it may extend into the smaller bronchi and bronchioles to produce the so-called capillary bronchitis or bronchiolitis. This may rarely lead to death from suffocation because of accumulation of exudate in the bronchioles, but is more often of importance because it may be the preliminary stage of a bronchopneumonia. Whereas in the larger bronchi there is an accumulation of exudate and desquamated epithelium upon the surface, in the smaller bronchi and bronchioles a similar amount of exudate may restrict the lumen very considerably. Acute fibrinous bronchitis is usually the result of extension downward from a laryngeal diphtheria and shows the fibrinous exudate extending through many ramifications of the bronchi. The histological examination shows the usual picture of acute fibrinous inflammations which in the smaller bronchi may extend laterally and involve the peribronchial lymphatics. Either by aspiration or by direct extension a fibrinous bronchopneumonia may be produced. A fibrinous bronchitis of the smaller bronchi and bronchioles may result from extension into the bronchi of a fibrinous pneumonia. Very rare cases of acute fibrinous bronchitis of unknown origin are reported which extend widely throughout the bronchi and produce fibrinous casts of the tubes. Acute purulent bronchitis may follow acute catarrhal bronchitis, usually because of severe infection by pyogenic bacteria. Acute gangrenous bronchitis may follow any of the forms enumerated. This is due to invasion by saprophytic organisms. The process invades the wall of the bronchi, with subsequent necrosis, and produces by its destruction of cartilage and muscle, as well as the sloughing out of necrotic material, a local or widespread acute dilatation or bronchiectasis.

Chronic Bronchitis.—This is usually of the catarrhal variety and may be the sequence of repeated attacks of acute bronchitis, the result of prolonged inhalation of irritant gases and dusts, the result of passive hyperemia due to heart disease, emphysema, vascular and renal disease, pulmonary tuberculosis, more especially the chronic ulcerative form which is almost always accompanied by a chronic catarrhal bronchitis. Grossly, the mucosa is thick, dense, and especially in those cases due to passive hyperemia, is red. The longitudinal markings of the muscle seen through the mucosa are usually obscured and sometimes thickening may be so great as to obscure the transverse markings of the cartilages. The mucosa is covered with a thick, tenacious, mucinous or mucopurulent exudate, and sometimes, more especially when due to passive

hyperemia, intermingled with blood. Histologically, there is a rich infiltration of lymphoid cells in the epithelial and connective tissues, usually with a considerable overgrowth of fibrous connective tissue, and in the cases due to chronic passive hyperemia there may be interstitial hemorrhage and hemosiderin pigmentation. The mucous glands are the seat either of marked mucoid degeneration or may be atrophic.

Bronchial asthma is characterized by paroxysmal attacks of dyspnea more prominent in expiration. The sputum often contains the Curschmann spirals of mucus, desquamated epithelium with moving cilia, mononuclear eosinophiles and sometimes Charcot-Leyden crystals. Some of the cases can be shown to be due to hypersusceptibility to inhaled, ingested or injected proteins, but some are apparently due to inhalation of large quantities of insoluble dusts or to chronic inflammations of the upper respiratory tract, incident to such abnormalities as deflected nasal septum, nasal polyps, enlarged tonsils, etc. Occurring in early life it is usually due to ingestion of foods, such as milk or eggs, later either to foods or bacterial infection and, in middle age or later, to bacterial infection (Walker). With the bacterial infection there is some hypersusceptibility to the bacterial proteins, although it is possible that the absorption of bacterial products may stimulate bronchial muscle to spasm. Asthma due to parenteral injections of proteins such as horse serum may occur at any time of life, as is true also of that due to inhalation of pollens and animal effluvia. Physiologically, the stimulus to muscle contraction occurs presumably by action upon the nerve muscle plates or nerve termini, of the substance to which the individual is sensitive. The question as to whether this is due to a toxic substance formed within the body at the time of absorption or some other mechanism is adequately discussed in the texts on immunology. There is also increased secretion of mucus and formation of edema which add to the respiratory difficulty.

According to the studies of Huber and Koessler, the process in man affects principally bronchi of medium and small size more than 0.2 mm. in diameter. There is "increased thickness of all layers from the epithelium to the outer fibrocartilaginous layer." The muscle shows constriction and true hypertrophy. The surface epithelium is often the seat of cloudy swelling and of desquamation and necrosis, covered with a mucous exudate containing lymphoid cells, leucocytes, mononuclear eosinophiles and desquamated epithelium. The glands are large, active and show rich content of mucin. The connective tissues are infiltrated with lymphoid and mononuclear eosinophilic cells, leucocytes, endothelial cells and in the cases of long duration there is fibrous hyperplasia. Grossly, the lungs may show emphysema due to repeated expiratory spasm, or local areas of atelectasis due to absorption of air behind obstructed bronchi or bronchioles. The larger bronchi are of little significance grossly, unless there be an associated or causative chronic bronchitis. The smaller bronchi are sometimes seen to be thickened.

Bronchial Stenosis.—Obstruction to the flow of air to the bronchial system may be due to influences operating within the bronchial wall, pressure from

without, and foreign substances in the lumen. The bronchial wall may be reduced in calibre, by scars of old ulcers, particularly those of syphilitic and tuberculous nature, and by tumors involving the walls. Of significance in the smaller bronchi is hypertrophy incident to bronchial asthma; either acute or chronic inflammations of the bronchial wall may be so marked as to produce complete occlusion of small divisions. Pressure from without may be the result of disease of the lymph nodes including anthracosis, tuberculosis and tumor involvement, tumors of the mediastinum and of the lung, tumors of the esophagus, and aneurysms of the aorta. The lumen may be seriously reduced by secretion and exudate originating within the bronchial tree. Foreign bodies include a wide variety of substances which may be aspirated under various circumstances, either as the result of carelessness in childhood, in insanity, or as particles of exudate from the upper respiratory tract. Such foreign bodies, if they remain in the bronchi, lead to inflammation because of bacterial contamination and may result in ulceration or in perforation with subsequent inflammation of the surrounding tissue. Bronchial perforation from aneurysms, abscess, gangrenous areas or tuberculosis of the lungs, pigmented or tuberculous lymph nodes, tumor masses in the lung or lymph nodes, and cancer of the esophagus, may lead to the presence in the bronchi of blood, pus, caseous material, necrotic tissue, tumor masses, or swallowed food. Partial obstruction may lead to alveolar emphysema; complete obstruction usually causes local atelectasis because of absorption of air in the lung.

Bronchiectasis, which signifies dilatation of the bronchi, may be saccular or cylindrical. It may be congenital or acquired, and may be diffuse or focalized. It may be of spindle form or, if a series of sacs be present, it may be varicose. The more acute forms of bronchiectasis are due to destructive disease of the wall such as described above under the heading of acute gangrenous bronchitis. The same may be true of acute purulent bronchitis. Such dilatations are due almost entirely to the disease of the wall and not contributed to in any large measure by increased intrabronchial air pressure. The usual chronic forms of bronchiectasis are commonly associated with a chronic catarrhal bronchitis which may undergo secondary changes following the dilatation. The diffuse form of bronchiectasis is usually cylindrical in character and affects particularly the lower lobes of the lungs. The involved lung is nodular to the touch and upon section shows the dilated bronchi, which contain secretion or exudate, depending upon the nature and duration of the disease. In the saccular variety the sacs are usually small, but may attain considerable size; the lesions are usually confined to one or both upper lobes. Histologically, the dilated bronchi are the seat of a more or less severe chronic bronchitis. The mucous membrane usually shows a chronic atrophic catarrh, although occasional cases occur in which the catarrh is hypertrophic, sometimes with the formation of folds of thickened mucous membrane. The connective tissue is infiltrated with lymphoid and plasma cells and in the later stages shows considerable fibrous hyperplasia. The epithelium may in some instances, more particularly in the saccular form, show metaplasia with the formation of squamous epithelium.

In the advanced cases there may be marked atrophy of the epithelium and of the glands and also of muscle and even of cartilage, so that the tube or sac is formed of a fibrous wall lined by epithelium. The material within the bronchi may be simply a thick viscid mucus, mucopurulent material or pus. The movement of this material is limited by the enlargement of the bronchus and is susceptible to invasion by saprophytic organisms, and the mass and the breath have an extremely foul odor. With suppuration and with rich invasion of saprophytic bacteria, ulceration and even perforation of the bronchial wall may occur.

Many cases of bronchiectasis originate in a chronic catarrhal bronchitis and two factors are probably of importance. The chronic cough of the bronchitis produces repeated increases of intrabronchial air pressure during expiration. This operates upon a bronchial wall somewhat weakened by the chronic inflammatory process and thereby leads to dilatation. Accumulation of secretion behind points of obstruction in bronchi may also lead to local dilatation. In cases of chronic interstitial pneumonia with great overgrowth of fibrous tissue in the lung substance, accompanied by fibrous adhesions between the two layers of the pleura, the outward movement of the thoracic wall during inspiration may produce sufficient traction upon bronchi to lead to dilatation. In limited areas this produces a saccular dilatation but may also, when widespread, lead to cylindrical dilatation. Foreign bodies may lead to localized dilatation due to acute inflammation and destruction of the bronchial wall in the neighborhood. The cross section of a lung the seat of collapse, may give the appearance of dilatation of the bronchi which, however, is only relative to the size of the compressed or collapsed lung. This must not be confused with true bronchiectasis.

The congenital forms of bronchiectasis are of two main varieties. In the one form there is usually failure of development of the alveolar sacs associated with enlargement of the members of the bronchial tree. This is usually a cylindrical enlargement with little or no inflammation of the bronchi. It is ordinarily discovered only accidentally, rather than because of any symptoms, and as a rule is limited to one lobe although it may be more widespread. In the other form such as that described by Koeckert, the alveoli show complete failure of development and the bronchus grows out from the primary tube as an extremely thin walled, cyst-like mass replacing an entire lobe or an entire lung. It is therefore a balloon-like distention of an improperly developed large bronchus. It is lined by cylindrical epithelium, and shows in its wall isolated areas of cartilage and of muscle. If very extensive the condition is not consistent with life.

Tuberculosis.—Miliary tubercles in the mucous and submucous tissues of the bronchi are not uncommon but are more likely to appear in cases of chronic ulcerative tuberculosis than in other varieties of the disease. These are apparently due to superficial infection by discharges from the cavity but may also be caused by blood or lymphatic dissemination. They sometimes fuse to form conglomerate masses but this is unusual. The miliary or conglomerate

tubercles may break through the mucous surface to produce small ulcers. In caseous bronchitis the wall may or may not show definite tubercles, but the lumen is more or less filled with an exudate made up of lymphoid, endothelial and desquamated epithelial cells, and the mass rapidly undergoes caseous necrosis. This is especially common in cases of caseous pneumonia where it involves small bronchi and bronchioles. It may, however, appear in the larger bronchi, and we have observed one case in which the caseous mass completely occluded the bronchial tree as far as the opening of the main bronchus. When involving the larger bronchi, the epithelium is more or less desquamated and degenerate, the connective tissue is the seat of a subacute or a chronic inflammation and miliary tubercles may be observed. The process may extend through the bronchial walls and produce a caseous necrosis of the surrounding lung tissue. When affecting smaller bronchi, the lesion may become fibrosed and sometimes completely surrounded by a fibrous capsule.

Syphilis may affect the smaller bronchi and main bronchi in essentially the same way as the trachea. The same is true of other granulomata.

LUNGS

Congenital Malformations.—The most significant malformations affecting the lungs are those which really originate in the bronchi. Variations in the number and arrangement of lobes are not uncommon and inferior accessory lobes upon either or both sides are frequent. Occasionally, faults in development in alveoli are observed and we have seen one case in which throughout both lungs almost all the alveoli were sacs 1 mm. or more in diameter, supported on an excess of connective tissue. One case was observed in our laboratory where there was complete absence of one lung and death was due to lodgment of a peanut in the main bronchus of the opposite lung. Most cases of faults of development of the alveoli are due to congenital syphilis. Accessory portions of lungs may be found in various parts of the thorax and indeed in the upper part of the abdomen.

Atelectasis.—This term signifies collapse of an entire lung or part of the lung. The term collapse is often restricted to those cases in which it is known that the alveoli have previously been air-containing. A lung the seat of atelectasis is reduced in size, and increased in specific gravity and consistence. The gray color of the normal lung is due in large part to the content of air and in atelectasis the color is dark red because of the relative increase in blood content. Since the lung does not expand and collapse as in normal respiration, a certain amount of stagnation of blood occurs and the color may be blue or purple. The organ is flabby, airless and of leathery consistence. If the condition persist for a considerable time there may be an overgrowth of connective tissue so that the density and firmness and resistance to cutting increase considerably. Histologically, the principle change is marked reduction in size of the alveoli accompanied as a rule by an increased amount of blood in the capillaries, veins and sometimes in the arteries. When of longer duration this may be accompanied by hemosiderin pigmentation. Fibrosis begins in

the supporting connective tissue of the lungs, and with atrophy and disappearance of alveolar epithelium there may be fibrous replacement of the alveoli. The same description applies to local areas of atelectasis, usually due to complete obstruction of a bronchus. The passive hyperemia may lead not only to pigmentation and fibrosis but also to edema and in some instances to a hypostatic bronchopneumonia. Atelectasis may be found in the new born as the result of failure of air to gain access to the alveoli. Judging from appearances at autopsies, it seems probable that several weeks elapse before the lungs are entirely expanded, for in infants it is common to find small areas of atelectasis in an otherwise well distended lung. The most important form of atelectasis in postfetal life is that due to compression. Usually this is the result of accumulation of fluid or air in the pleura, including the transudate of edema, exudates of inflammatory character and air which may gain access through rupture of the lung, or by traumatic perforation of the thoracic wall. Tumors in the pleura produce the same results. Tumors of the mediastinum, thoracic aneurysm and extreme enlargement of the heart may also compress the lung. Deformity of the thorax, such as that produced by kyphoscoliosis of the thoracic spine, may lead to moderate degrees of compression atelectasis. The same is true of temporary or permanent deformity of the thorax due to pushing of the diaphragm upward by such conditions as ascites, gaseous distention of the stomach and intestines and abdominal tumors and swellings. Localized areas of atelectasis of the acquired variety are usually due to obstruction in the bronchial tree, such as may be due to foreign bodies, exudates and inflammatory swelling of the mucous membranes, etc. The air in the obstructed portion is gradually absorbed by the circulating fluid, presumably first the oxygen, then the carbon dioxide and then the nitrogen.

The important functional significance of atelectasis is seen in reduced vital capacity and in failure or reduction of gas interchange in the affected part of the lung. Owing to the large factor of safety in functional capacity of the lung, important manifestations due to these changes are not observed unless the collapse is extensive. Sudden collapse may produce symptoms, but in the majority of cases these soon disappear owing to compensation. The fact that in chronic disease of the lung a considerable part of the tissue may be destroyed, and in experimental work as much as five-sixths of the lung may be removed and that in both instances the condition is compatible with normal life, indicates the great reserve capacity of these organs. In compression atelectasis the return of blood to the left heart is somewhat reduced, so that in the general circulation there may be a fall in mean pressure and in pulse pressure.

Acute Massive Atelectasis.—Since attention was drawn to this condition, as massive collapse of the lung, by W. Pasteur, it has been found to be a not uncommon postoperative complication. It may complicate peritonitis and the paralyzes of diphtheria. Anatomically there is collapse of the air cells of the lung, usually unilateral but sometimes bilateral, extensive and often involving an entire lung. The heart and mediastinum are displaced toward the affected side. Pasteur suggested a neurogenic origin; Scott says "it appears

to be a reflex blocking of finer air passages in the affected lung tissue, quite possibly of vasomotor origin," and Lee noted two factors, "embarrassment or paralysis of the respiratory movements and obstruction of the bronchial tubes."

Emphysema.—This term signifies an increase in the air containing capacity of the lung. The acute form of pulmonary emphysema is merely an overdistention of the lung. It has a striking exemplification in acute distention of the lungs of the guinea pig in anaphylactic shock. In man the same condition may be met in acute anaphylactic death. It is also seen in death from drowning, traumatic asphyxia and sometimes in asphyxial death from bronchitis of various forms. The lung is distended and pale, but in man can be reduced to normal volume by compression. Histologically, there is simply distention of the alveoli, with such special addition to the picture as may be produced by particular causes. The term emphysema ordinarily conveys the impression of more serious change in the lung substance, especially in the form of loss of elasticity and rupture of alveolar walls. There are three great forms to consider, namely, the chronic or essential pulmonary emphysema, senile emphysema and interstitial emphysema, the last of which is acute.

Chronic Pulmonary Emphysema.—This is essentially a dilatation of the alveolar spaces associated with rupture of their walls. Two important physical factors must be concerned; namely, an increase in the positive pressure in the alveolar spaces or a weakening of the alveolar walls. Practically all the known causes of chronic emphysema involve expiratory efforts against resistance and therefore an increase in positive pressure within the alveoli during expiration. The condition is observed in players upon wind instruments, particularly the brasses, glass blowers and in other similar occupations, and in victims of chronic long standing cough. The repeated and prolonged distention results in loss of elasticity, probably due to atrophy and even rupture of elastic fibers. There must then be compression of interalveolar capillaries which leads to thrombosis in these vessels and reduction of nutrition to the alveolar walls. This is followed by rupture. It is assumed that thrombosis must have existed because hemorrhage is not likely to occur during the course of the disease, except occasionally in its late stages. Therefore, there is involved in the process an increase in positive pressure during expiration and a subsequent weakening of the alveolar walls.

Grossly, the lung is considerably enlarged and the condition is often called large-lung emphysema. The surface is pale because of the increase of air content, the reduced capillary circulation and the separation of anthracotic areas. Even to the naked eye the enlarged alveoli are plainly visible, looking like small gas bubbles. The lung is of cottony consistence, resists compression and does not collapse materially upon opening the thorax. Since the sharp margins of the lung are less well supported against the increased intra-alveolar pressure than are the other parts of the lung, fusion of the alveoli in this situation may produce large air containing blebs called bullous emphysema. The organ cuts with normal or slightly increased resistance and shows a pallid, relatively dry cut surface in which individual alveoli are easily visible. Micro-

scopically, the alveoli are large and their walls thin. Projecting into the margins of the vesicular spaces are small spurs representing the remnants of ruptured alveolar walls. Fibrosis of interstitial connective tissue can often be made out in the less distended parts and special stains show reduction in the amount of elastica. Chronic catarrhal bronchitis is a frequent accompaniment. Interference with circulation may be marked, so that in the terminal



FIG. 241—Emphysema of lungs showing well marked bullous emphysema at the margins.

stages passive hyperemia may be severe both grossly and microscopically, and there may be the usual changes accompanying passive hyperemia.

The chest of such patients is large and shows reduced motility. This factor, together with the reduced elasticity of the lungs, results in an increase in the dead space and a decrease of vital capacity. This leads to deficient ventilation within the lungs, which may be in part compensated for by increase in the rate of respiration. The alveolar air contains unusually large quantities

of carbon dioxide and the same is true of the blood. As Scott has shown, such patients are extremely resistant to increases in carbon dioxide in inspired air, and whether or not this be due to alteration in sensitivity of the respiratory center, it can be stated very simply that the blood may show much more carbon dioxide without respiratory symptoms than in normal individuals. In discussing polycythemia it was pointed out that such alteration of ventilation in the lung may lead to increase in the circulating red cells and, as Price-Jones has indicated, an increase in their individual size. The limitation of expansion and collapse of the lungs and the loss of pulmonary elasticity remove definite aids to pulmonary circulation. Stagnation is further favored by the obliteration of pulmonary capillaries. These factors lead to hypertrophy of the right heart, whose failure is followed by passive hyperemia. Even with mechanical adequacy of circulation the reduction of capillary area results in a reduced gas interchange in the pulmonary blood, observed principally as an increase in content of carbon dioxide.

Senile Emphysema.—This is a small-lung type of emphysema occurring in aged individuals, and due primarily to senile atrophy of the alveolar walls rather than to absolute increase in intra-alveolar pressure during expiration. With the atrophy and weakening of the walls, normal respiratory pressures apparently are sufficient to produce rupture. Owing to the decrease in capillary content the lung is likely to be pale and because of the fusion of the alveoli by rupture of their walls, they may be clearly visible to the naked eye. Sometimes the large-lung type of emphysema is referred to as hypertrophic emphysema and the small-lung type as atrophic emphysema. Since the underlying condition in both is atrophy of the alveolar walls the term hypertrophic should be abandoned. There are none of the factors essential to hypertrophy in any of the forms of pulmonary emphysema.

"Compensatory" Emphysema.—It is not uncommon to find areas of emphysema in the neighborhood of atelectasis. Furthermore, it is extremely common to find in cases of chronic lung disease such as tuberculosis associated with destruction of considerable lung tissue, emphysema of the remaining parts. It is probable that in all these cases the emphysema is a chronic pulmonary emphysema due to persistent cough, in other words, simply a local or fairly widespread manifestation of the condition described above as chronic pulmonary emphysema. Knowing the reduced functional capacity of emphysematous lungs, it is incorrect to regard this process as in any sense truly compensatory.

Interstitial Emphysema.—This term signifies the presence of air in the interstitial tissue of the lungs. The air may gain access to the interstitial tissue by rupture of the alveolar walls by violent coughing, such as may occur in pertussis or other acute respiratory infection. The condition is more common in children, whose lungs are less resistant to strain, than in adults. Traumatic tearing of the lungs may result from needle punctures, fractures of the ribs, stab wounds, bullet wounds, etc. The air is present in bubbles of various sizes situated in the interstitial tissue and underneath the pleura between the

anatomical lobules. Sometimes it extends into the mediastinal connective tissues and may follow the cervical fascias up into the neck. In some cases it may extend down over the chest and even as far as the abdominal wall. The admission of air to the pleural cavity by needle puncture or other wounds, may produce emphysema of the subcutaneous parts in the neighborhood of the wounds because of expression of the air into wounded tissues during respiratory movements. This condition does not necessarily presuppose actual penetration of the lung itself. Wounds of bronchi, and of the trachea, as for example in tracheotomy, may lead to pulmonary interstitial emphysema.

Circulatory Disturbances. Active Hyperemia.—The inhalation of irritant gases, of irritant dusts, and the presence of early stages of acute inflammation produce active hyperemia in the lungs. Reduction of barometric pressure such as occurs in aviation may also produce active hyperemia. The circulation in the lungs is maintained in part by the regularity of the respiratory movement, and interruptions such as occur in hanging or other varieties of asphyxia may result in an active hyperemia which in some instances is accompanied by hemorrhage. If the lung be compressed by fluid in the thorax and this be rapidly removed, the inflow of blood into the lungs is accelerated and active hyperemia results. This may lead to edema of the lungs which in occasional instances is so severe as to be fatal.

Passive Hyperemia.—Examination of the lungs at autopsy practically always shows a considerable accumulation of blood in the dependent parts of the lower lobes. This is a relatively acute form of passive hyperemia incident to failure of the circulation shortly before death. The affected portions of the lung are dark red or purple, somewhat firmer and less crepitant than normal. If the condition persist for a considerable length of time there may be small hemorrhages into the alveoli, edema, and sometimes a bronchopneumonia, referred to as hypostatic bronchopneumonia. Much more important pathologically and clinically are those forms of passive hyperemia which are of considerable duration and involve the entire lung. Outstanding among the causes of this condition is mitral stenosis, which may produce a passive hyperemia extending over years. Aortic stenosis may produce essentially the same condition because of incomplete removal of blood from the left ventricle, with damming back in atrium and lungs. Other valvular lesions are of importance only when the heart or the valve orifices dilate. In the early stages, the lung is large, dark red or purple in color, somewhat firmer and with less crepitation than normal. Histologically, the capillaries as well as veins are distended with blood. Small hemorrhages, edema, and hemosiderin pigmentation in endothelial cells may accompany the passive hyperemia. The more chronic forms are characteristically described as "brown induration." The color is caused by deposit of hemosiderin in the lung, and the increased consistence by overgrowth of connective tissue. Grossly, the lung does not collapse readily when the thorax is opened, is large, firm and of reddish-brown color. It cuts with increased resistance and shows a firm, dark red or reddish-brown, freely bleeding, moist cut surface. Histologically, there is distinct overgrowth of

connective tissue involving the alveolar walls and the other interstitial supporting connective tissue framework. Capillaries and veins are filled and distended with blood. Within many of the alveoli there are typical heart failure cells, large mononuclear endothelial cells containing fine golden brown granules of hemosiderin, which under proper conditions gives the iron reaction. Similar cells often accumulate in lymphatic spaces around the blood vessels and bronchi, and pigment may also be found free in the tissue spaces. As has been explained in the chapter on disturbances of circulation, the pigment is due to the presence in the alveoli of red blood corpuscles which undergo degeneration with the production of hemosiderin, and this is phagocytosed by

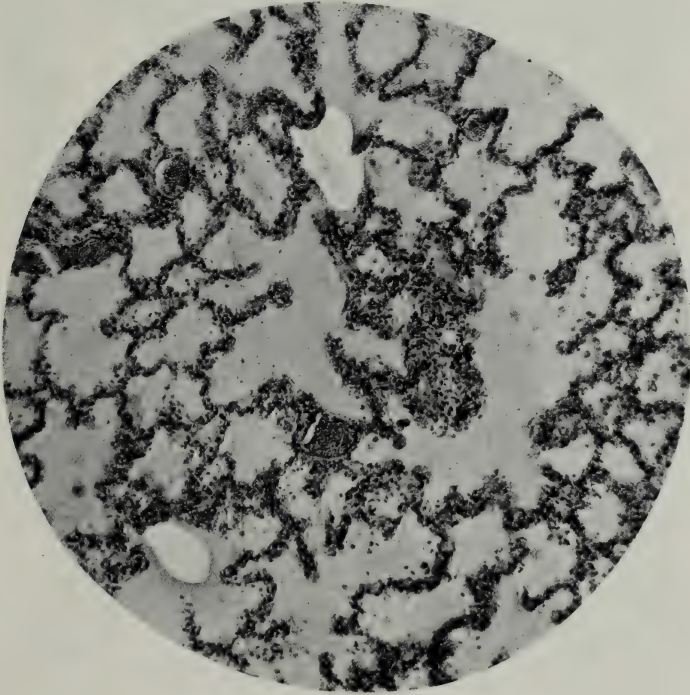


FIG. 242—Pulmonary edema with hyaline type of precipitate in the alveoli (Phosgene gas). Army Medical Museum, 4992.

the wandering endothelial cells. These may remain in the alveoli or enter the lymphatic tracts and the pigment may be transported to mediastinal lymph nodes. The alveoli may contain free red blood corpuscles and often show edema. The bronchi are usually the seat of a chronic bronchitis. The pulmonary artery both grossly and microscopically frequently shows an intimal arteriosclerosis. Although the cause of this arteriosclerosis is not definitely known, nevertheless, the impeded circulation through the lung followed by hypertrophy of the right heart, produces increased pressure in the pulmonary arteries and probably has some direct influence upon the production of the pulmonary arteriosclerosis. Occasionally, the alveoli contain concentrically laminated, radially striated corpora amylacea. Physiologically, victims of

chronic passive hyperemia of the lungs show a reduced vital capacity, probably due in part to the reduction in size of the alveoli by fibrosis of their walls, and consequent limitation of their movements, and also due to the presence of edema, which is a common accompaniment.

Pulmonary Edema.—This may be a transudate or may be of inflammatory origin. The transudates are usually due to failure of the circulation in the lung. This results principally from cardiac disease but may also be due to pulmonary disease, to compression from substances in the pleural cavity, not infrequently accompanies nephritis, and experimentally may be produced by

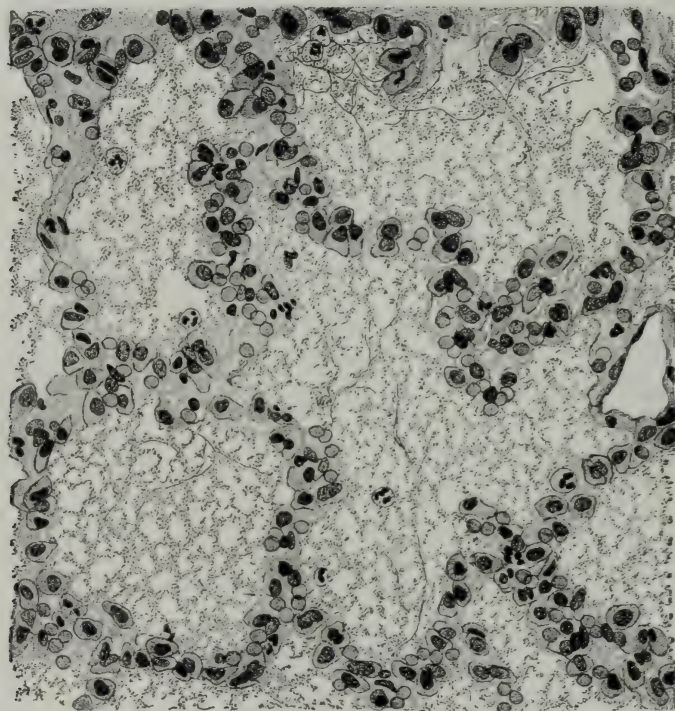


FIG. 243—Pulmonary edema, showing granular type of precipitate in the alveoli.

injections of large quantities of adrenalin and by irritation of the vasomotors of the pulmonary circulation. The circulation may be so disturbed following rapid withdrawal of fluid from the pleura as to cause pulmonary edema. Irritant gases also produce edema and this has been found to be especially true of certain war gases such as phosgene and chlorpicrin. When due to passive hyperemia, it is possible that there is a combination of the high pressure on the pulmonary capillaries and increased permeability of their walls owing to reduced nutrition. In other instances, it appears that increased permeability is of considerably greater importance, especially where toxic factors are concerned. The lung of edema is large, pallid, pits upon pressure and sometimes is so firm as to suggest consolidation. Upon cutting, considerable frothy

fluid pours out from the wet cut surface and may occupy parts of the bronchial tree. Depending upon the degree of associated hyperemia, the fluid may be colorless, salmon colored or red. In lesser degrees of edema it is necessary to press upon the lung so as to express the edema fluid. The histological character of the fluid in the alveoli depends upon its content of protein and the method of fixation. It may appear either as a delicate hyaline sheet of faintly acidophilic material or as a finely granular acidophilic material. It may partly or completely fill the alveoli and extend into the infundibuli and the bronchi. Minute air bubbles are sometimes observed.

The presence of edema reduces the vital capacity and interferes with interchange of gases in the alveoli. The fact that it so commonly appears as a terminal event suggests that it is the direct cause of death. Certainly, if edema be extensive, the functional disturbance is great, but the experiments of Winternitz and Lambert make it seem probable that much larger amounts of fluid than are ordinarily observed are necessary in order to produce death.

Inflammatory edema appears in the early stage, and may also appear at any time during the course of, lobar pneumonia. It is also commonly present around areas of bronchopneumonia, of abscess, gangrene, and other inflammatory conditions in the lung. Histologically, it may be designated as inflammatory because of its position in reference to definitely inflammatory conditions, but may show no other characteristic features. Because of its larger protein content it is likely to stain more deeply than the non-inflammatory forms. More especially in lobar pneumonia its content of fibrin gives it a distinguishing character.

Hemorrhage.—Blood may appear in the lungs because of aspiration from hemorrhages in the upper respiratory tract, or from blood of the stomach which has been vomited and aspirated. Perforation of aneurysms into bronchi is a common cause of blood in the lungs. Hemorrhage may occur into the pulmonary tissue as the result of traumatism and the destruction of lung substance by inflammatory or tumor involvement. When pneumonia complicates hemorrhagic or "black" infectious diseases, the exudate may be of hemorrhagic character. Passive hyperemia, asphyxia, and the hemorrhagic diseases such as purpura may lead to hemorrhage in the lung. Of great practical importance is that variety due to erosion of blood vessels by chronic ulcerative tuberculosis, where hemorrhage may be severe and fatal.

Pulmonary Embolism.—This may be of two important varieties; one the form in which large areas of circulation are occluded, and the other in which only small areas are occluded with the production of minute circulatory disturbances or infarction. The former variety is a common cause of death following operation, whether septic or aseptic, or as the result of traumatism with subsequent venous thrombosis, or of areas of infection and associated thrombosis within various parts of the body. Owing to dislodgment or disintegration of thrombi, an embolus may pass through the right heart and lodge in a large branch of the pulmonary artery. The same general effect may be produced by the lodgment of multiple emboli in smaller arteries. Death may

ensue immediately, within the course of a few hours, or after the course of eighteen or twenty-four hours, and occasional cases of embolism recover (Schumacher, Mann). Immediate death is probably due to intrathoracic reflex inhibition of the heart. Later death may be due to shock, and some

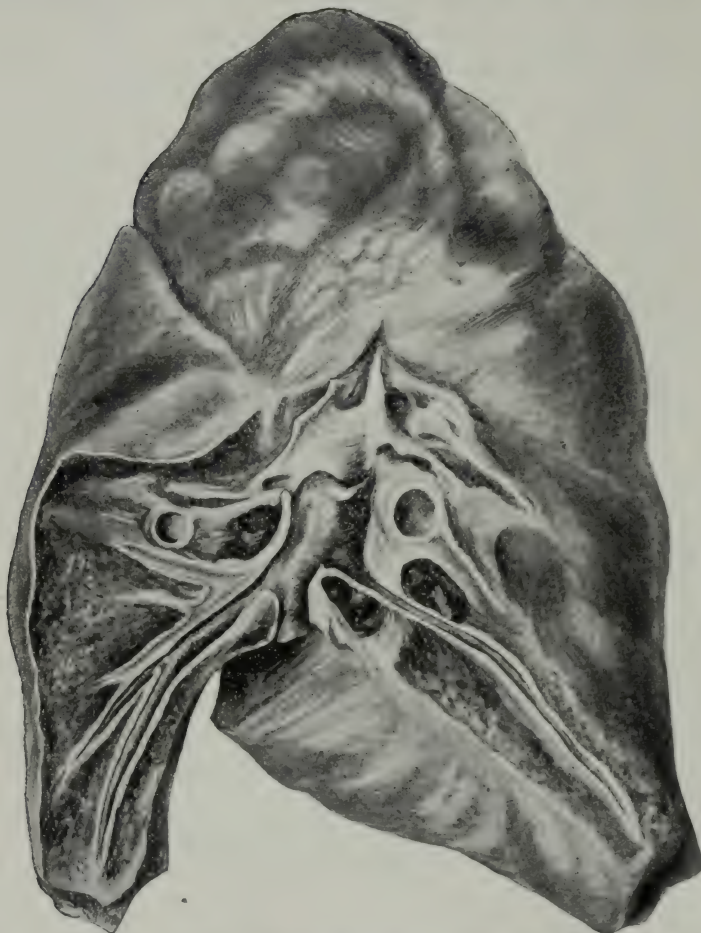


FIG. 244—Dissection showing embolism of the pulmonary artery.

cases probably meet death because of asphyxia due to interference with a large area of pulmonary circulation. In order satisfactorily to demonstrate pulmonary embolism at autopsy, the pulmonary artery from the right heart onward must be opened before removal of the heart from the body. The embolus differs from the ordinary postmortem clot in that it is fairly firm, somewhat friable and mottled in character. Secondary red clots may extend in both directions from the primary embolus. The lungs are usually the seat of considerable passive hyperemia which is due to the embarrassment of cardiac action, owing to extensive obstruction in the pulmonary circulation rather than to the embolism itself.

Embolism of smaller pulmonary arteries does not produce infarction, as

we have shown, unless there be a coincident passive hyperemia of the lung. In experiments upon dogs we found that several weeks after occlusion of a small branch of the pulmonary artery there was an area of slight cyanosis, conical in form, corresponding to the distribution of the pulmonary artery but neither necrotic nor hemorrhagic. The clinical investigations of Cutler and Hunt would indicate that some of the pulmonary complications following anesthesia are the result of embolism without infarction, although the latter may occur. These areas show distinct hyperemia and a reduction in the size of alveoli, may be edematous but do not show necrosis of the alveolar walls.

Pulmonary emboli usually originate in thrombi in the right side of the heart or in the venous system. In the latter situation thrombosis may result from a variety of causes including surgical and other forms of trauma, local or general infections, the latter including typhoid fever. Important veins of origin are those of the pelvis, genitalia, lower extremities and abdominal cavity. It is possible that with a patent foramen ovale, emboli from the left heart may enter the pulmonary circuit. Small emboli occlude small vessels. The larger vessels are usually occluded by long narrow emboli which, as they lodge, become coiled or twisted so as to occupy a larger lateral diameter. Secondary changes occur as in thrombosis generally. If the embolus be infected, abscess or infected infarcts occur.

Fragments of tumors which invade veins may lodge as emboli in the pulmonary arteries and subsequently produce secondary tumors. If associated passive hyperemia be present, infarction occurs.

Fat emboli are especially likely to lodge in the pulmonary vessels. The general circulatory effects have been discussed in the chapter on disturbances of circulation. Grossly, the lungs show little of significance except moderate or severe degrees of hyperemia and edema. Histologically, there are hyperemia and edema, sometimes small intra-alveolar hemorrhages, and, with frozen section and special stains, droplets or cylinders of oil in the capillaries and smaller arteries and veins. Not infrequently rupture of capillaries and alveolar walls leads to the presence of oil in the alveoli. As has been indicated in the chapter on circulation, fractures of bones, and operations through fat tissue, etc., often produce slight fat embolism, easily demonstrable but not quantitatively sufficient to produce death.

Pulmonary Infarction.—At autopsy infarcts of the lung are almost always hemorrhagic. They are usually moderate in size not exceeding 3 or 4 cm. in diameter, and occur most commonly in the lower lobes although larger infarcts and infarcts in other position are not infrequent. They are usually due to emboli whose source can readily be ascertained, but occasional cases occur, particularly in chronic heart disease and in chronic kidney disease, where the lesions appear to be due to thrombosis primary in the pulmonary artery. Experimental studies indicate that passive hyperemia of the lung is necessary in order that an embolus may produce infarction, and in human medicine infarction is practically always associated with passive hyperemia due either to chronic cardiovascular disease, to local venous obstruction, to poor pul-

monary drainage or to compression of the lung by fluid, tumors, and air in the pleural cavity, or any of the causes discussed above in connection with atelectasis. The pulmonary capillaries come out so directly from the smaller arteries and arterioles that following embolism, circulation in the affected areas is adequate to prevent necrosis unless the collateral circulation is interfered with by passive hyperemia. Our studies have shown that following the embolism there is hyperemia in the area supplied by the obstructed vessel. Hemorrhage into the alveoli occurs because of increased permeability of the capillary wall due to degeneration and necrosis. Edema is likely to appear before hemorrhage. In early infarcts marginal leucocyte infiltration and hyperemia may be observed, but as a rule the hyperemia is concealed by the general passive hyperemia of the lung. If the condition last long enough the infarcts undergo extensive necrosis, and decolorization of the contained blood. Subsequently, encapsulation or organization occurs, usually proceeding from the pleura, from the large connective tissue septa in the infarct, and from the non-infarcted lung in the margin. In man the white or decolorized infarcts are not often observed, because the general condition producing passive hyperemia and that which serves as an origin for the embolus usually determines death before decolorization occurs. White infarcts of the lung, however, have been observed. The hemorrhagic infarct is a generally conical area whose contour may be altered because of the fact that infarcts are common near the sharp edge of the lung. The area is swollen, dark red in color, sharply defined and solid. The cut section shows a generally triangular, well defined, bulging, solid, dark red, smooth, somewhat dry, friable cut surface. Not infrequently the embolus and its secondary thrombosis can be discovered in the affected artery. Histologically, the alveoli and bronchi are filled with blood. In early cases the alveolar walls and other structures of the lung are apparently well preserved, although search within the blood of the alveoli will show desquamated alveolar epithelium. Marginal leucocyte infiltration may be observed. Subsequently necrosis becomes more and more prominent, first in the alveolar walls and later in the bronchial and vascular walls. The white infarcts are of the same general character but show a brownish-white or yellow color. They are usually retracted rather than swollen and the cut surface shows the friable granular material of necrosis. Marginal fibrosis is also present and sometimes the area may be almost completely fibrosed. Wholly cicatrized infarcts of the lungs are rarely observed. The studies of Ghoreyeb and Karsner indicate that the bronchial artery plays no important part in the mechanism of pulmonary infarction.

Inflammations of the Lungs.—These may appear as exudates within the terminal bronchioles and alveoli or within the interstitial substance. Except for the suppurative forms, usually named abscess, inflammations of the lungs are referred to as pneumonia or pneumonitis. Two great divisions are recognized, namely, lobar, croupous or fibrinous pneumonia and broncho-, lobular or catarrhal pneumonia. The third form is interstitial pneumonia which may be acute or chronic. The pneumonias run a more or less characteristic course

with definite clinical signs and are general diseases, either primary in the lungs or secondary to some other focus of infection.

Lobar Pneumonia.—This is a more or less self-limited infectious disease with its principal anatomical manifestations in the lungs. It is usually of abrupt onset but may be preceded by a period of cough or coryza. Invasion is frank and the disease rapidly reaches its acme or fastigium, which remains for a period usually of seven to eleven days to be followed in half the cases by crisis and in the other half by lysis. Convalescence may be interrupted by a variety of complications.

The onset is often accompanied by chill and pain in the chest, followed by fever with its various phenomena, leucocytosis (polymorphonuclear), rapid respiration and other respiratory changes, physical signs, at first of moisture in the lungs and then of consolidation. When crisis occurs the temperature rapidly falls, often with signs of collapse, and the exudate undergoes solution. In order to render more clear the discussion of etiology and secondary effects, the morphology of the disease will be presented. Three stages are recognized in the lungs, engorgement, hepatization and resolution. Two substages of hepatization are recognized, red and gray. Resolution may be delayed, the exudate may become organized, or abscess or gangrene supervene.

The stage of engorgement is not often observed at autopsy except as part of the process of extension of the pneumonia. The conditions existing, however, are fairly well known as the result of anatomical studies, from inference and from comparison with experimental work. The area involved is not so sharply defined as in the later stages of hepatization but is more or less coextensive with one or more lobes of the lung, usually the lower lobe. The area involved is large, soft, red and flabby. From the red, smooth, moist, cut surface, blood flows and a considerable amount of edematous fluid can be expressed. Histologically, the smaller blood vessels and capillaries are found to be markedly engorged, and in the terminal parts of the bronchial tree and the alveoli there is edematous fluid with little or no fibrin but containing cells of the early exudate; namely, lymphoid cells, desquamated endothelium, endothelial cells, transitional cells, a few leucocytes and red blood corpuscles. The cells of the exudate, however, are very small in number. When bacteria are found they are in greater number in the finer bronchioles and infundibula.

The stage of hepatization includes red hepatization and gray hepatization, but it must be understood that the stage of red hepatization is of very short duration, probably rarely lasting more than one or two days and merging rapidly into gray hepatization. Often sharp distinction between the two is impossible and mixtures are observed. Grossly, this stage practically always shows a fibrinous exudate upon the pleura of that part of the lung consolidated. Although the consolidation is lobar in distribution and affects the right lower lobe more commonly than other lobes, nevertheless, it is common to find more than one lobe involved and the process extending to a limited degree into adjacent lobes. When affecting principally the lower lobes, the involvement of the middle and upper lobes is likely to present a horizontal upper limit in

reference to the standing posture. The involved portion is large, firm, and of red, gray, or mottled color, and often shows the indentations of ribs. Crepitation is entirely absent except that the margins may sometimes contain air. The lung cuts with somewhat reduced resistance and the cut surface is red,



FIG. 245—Gray hepatization of lobar pneumonia, showing also acute fibrinopurulent pleurisy. Army Medical Museum 501.

gray or mottled, and dry, somewhat more so in gray hepatization than in red hepatization. The dryness is not absolute but is relative to the uninvolved portion of the lung. The consolidated part is distinctly more friable than normal. The cut surface is definitely granular, due to the fact that the plugs of fibrinous exudate in the alveoli project above the retracted cut edges of alveoli and small air units. In gray hepatization the acute fibrinous pleurisy is

more advanced and is likely to show early organization. In addition, at this stage, there may be a moderate amount of fluid in the pleural cavity.

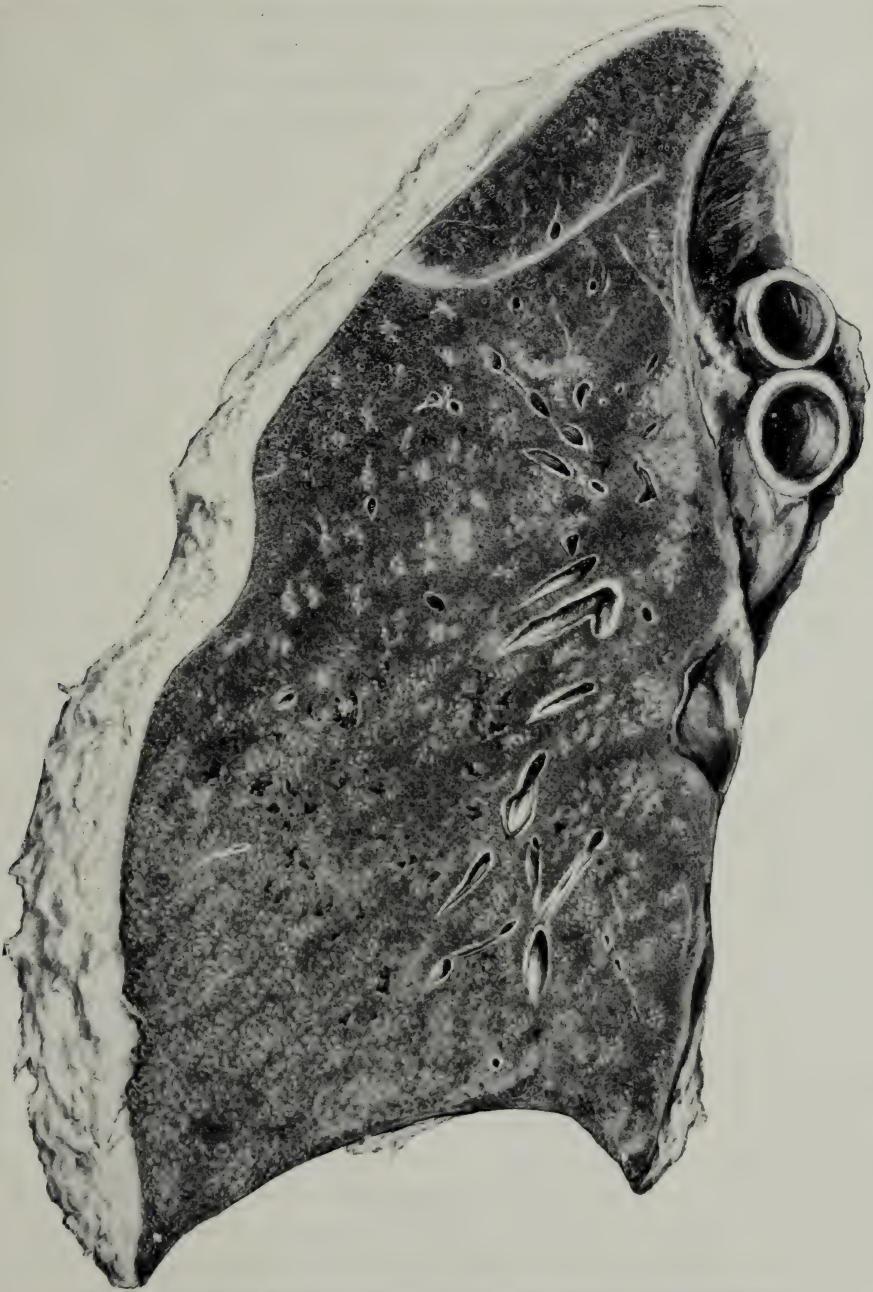


FIG. 246.—Drawing of gray hepatization of lobar pneumonia to show granular character of cut surface.

Histologically, the differentiation between the exudate of red and gray hepatization is usually readily recognized, but intermediate stages exist in which an exact diagnosis is not possible. Our summary of the histological

picture is based largely upon personal experience, aided by the critical studies of such workers as Pratt, Evans, Armstrong and Gaskell, and Permar. In the earlier stages exudation is most pronounced in the bronchioles where desquamation of epithelium, infiltration of lymphocytes, a few leucocytes, and large mononuclear cells, together with a moderate number of red blood corpuscles enmeshed in a fluid and fibrinous exudate, is prominent. During this stage the alveoli may show little more than fluid exudation, but rapidly the same type of exudate as that seen in the bronchioles involves the infundibula and the air cells. Even in the same section various stages of this process may be observed. Pneumococci are present throughout the exudate but in greatest number in the bronchioles. The smaller blood vessels and capillaries are the seat of intense hyperemia. The bronchi may or may not be involved in the process, but typically, they show no important lesion. In this stage of consolidation the cells are not densely packed in alveoli or bronchioles. In the stage of gray hepatization the cellular content of the exudate is vastly increased, so much so that the exudate is packed tightly within the alveoli, but according to Kline and Winternitz this does not explain the impaired circulation. The cells are principally polymorphonuclear leucocytes although a considerable number of small and large mononuclear cells may still be present. These cells may show phagocytosis of bacteria and cell fragments but never to any great extent. Red blood corpuscles, present in the stage of red hepatization in moderate numbers, are practically absent in gray hepatization except as shadow cells. The involvement is fairly uniform through the alveoli and the smaller members of the bronchial tree, more uniform than in red hepatization. At this time bacteria are numerous both in the bronchioles and in the alveoli. The arrangement of the fibrin in the alveoli is more or less characteristic in both stages although the appearance is more pronounced in the later stage. The strands are arranged irregularly but show a general disposition to radiate out from a point in the alveolar wall. The fibrin in adjacent alveoli communicates through small pores or holes in the wall, the pores of Cohn, thus giving the fibrin mass a double fan or hourglass arrangement. Miller believes the pores to be the result of desquamation of lining cells from the adjacent parts of neighboring alveoli. In the later stages of gray hepatization, near the period of resolution, although the pneumococci may be recovered culturally they are not easily demonstrated in tissue sections.

Resolution is characterized by the solution of the exudate. In the earlier stages the lung is still consolidated but is soft and flabby instead of firm. The pleural exudate is reduced in amount and loose adhesions may be present as the result of organization. The color of the mass is gray or yellow and in either case may be mottled with red. The lung cuts easily but the cut surface instead of being dry and granular is smooth and moist, and from it can be expressed a considerable amount of granular or somewhat slimy, semifluid remnants of the exudate. This may resemble pus grossly but is not pus. The lung substance is still friable. As the exudate is removed, partly by expectoration of the softened mass and more largely by absorption, the lung gradually

contains more and more air. The exudate is finally removed and save for moderate hyperemia lasting over a few weeks, the lung is restored to normal. Functionally, the vital capacity is wholly restored (Shepard). Histologically, there is necrosis of the leucocytes of the exudate and solution of the fibrin. Large endothelial phagocytes are likely to be present and contain fragments of leucocytes and fibrin. Fat is present in moderate amounts. Pneumococci are recoverable both in sputum and from the exudate but are not numerous in the histological section. The epithelium of the bronchioles and of the alveoli is renewed during the process of resolution. As far as can be determined by histological methods the ultimate restoration is absolutely to normal, although it is well known that an individual once the victim of pneumonia apparently is more susceptible to subsequent attacks of the same disease. The stage of resolution is practically coincident with the crisis or beginning lysis of the clinical disease.

Causes of Lobar Pneumonia.—Although pneumonia may spread fairly widely in given localities it is not likely to occur in great epidemics. It is more frequent in cities than in the country and in closely inhabited areas than in places where the population is dispersed. Indoor life in crowded conditions and in fact crowding under almost any circumstances, such as in institutions and in army encampments, appears to predispose to the disease. Occupations which lead to considerable variations in temperatures predispose. It may affect any period of life but is more common between twenty and forty years. It

attacks males more frequently than females, probably because of occupational and other influences rather than because of sex. Negroes appear to be more susceptible than whites but this may be due to hygienic conditions rather than to racial differences. It must be conceded, however, that perhaps a certain degree of racial immunity is developed through generations of exposure to the disease. Depraved nutrition, poor hygienic surroundings, alcoholism and exposure to cold appear to reduce resistance. There is little doubt that in some instances traumatism, especially of the chest, may predispose to lobar pneumonia. Pneumonia occasionally occurs after anesthesia but is usually bronchopneumonia, rather than lobar pneumonia, although the latter occasionally occurs. The disease, however, frequently attacks young individuals apparently in the midst of perfect health.

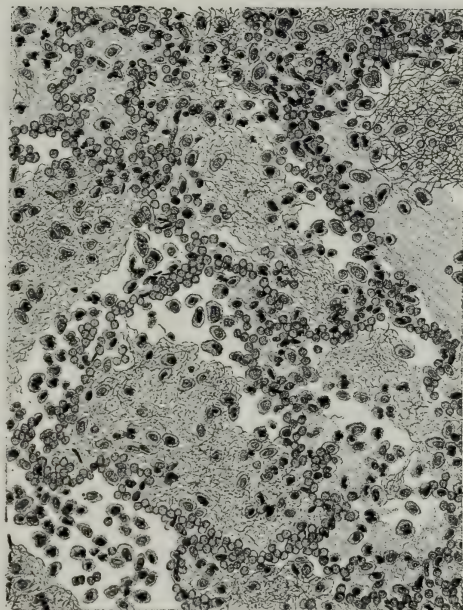


FIG. 247—Drawing of red hepatization to show the cellular character of the exudate and the fibrin.

The exciting cause of 90 per cent. of the cases, according to the statistics of Cecil, which do not vary materially from those of other investigators, is the diplococcus pneumoniae, the pneumococcus. Other causative organisms include the streptococcus hemolyticus, the streptococcus viridans, the bacillus influenzae, the bacillus of Friedlander, and the staphylococcus aureus, in the order named. In all large series of studies there remains a small number of cases, usually less than one per cent. in which the exciting cause cannot be positively identified. In the order of frequency of occurrence the disease is caused by pneumococcus type I, and then by type IV, type II and type III. Apparently type III is the most virulent.

Pathogenesis and Distribution—The pneumococcus is present in a large number of human throats without producing pathological changes. The organisms found, however, are usually of type IV, whereas this type is associated with only a fraction of active pneumonias. Thus, there is serious question as to the importance of the carrier state. Unless type IV can be changed to the other types, carriers must be of little significance and the infection must be spread from the active disease or during that period of convalescence when the homologous organism is recoverable. Therefore, transmission is probably by droplet infection, since, as Wood has shown, pneumococci live only a short time in dried powdered sputum. Whether the organisms are introduced from without or may represent changes of organisms already present, there is no doubt that certain of the predisposing causes noted above including particularly chilling, alcoholism and perhaps also traumatism, are of considerable importance. In experimental animals the work of Meltzer and his collaborators indicated that a large dose of organisms is necessary for infection. On the other hand, the work of Blake and Cecil shows that at least in monkeys small doses may produce extensive pneumonia. There must be some difference in the susceptibility of different species of animals to pneumonia. Stillman, and Dochez and Avery are of the opinion that the common throat organisms differ biologically from those of pneumonia. This is of importance not only in connection with the direct cause but also in the consideration of carriers. It is believed that the transfer of organisms from the outer air or from the upper respiratory tract is directly air borne to the more remote parts of the bronchial tree, but the studies of Winternitz, Smith and Robertson indicate that implantation of pneumococci into the structures of the upper trachea may lead to more remote distribution by lymphatic routes. Thus, it is possible that pneumococci may penetrate the mucosa of the upper trachea and thence be distributed by the lymphatics. For the present it must remain a question as to whether the spread from upper to lower respiratory tract is entirely air borne, entirely lymphatic borne, or a combination of the two modes. It is conceivable that blood transmission occurs, but if this were true positive blood cultures should be more common than they are. There is not adequate support for the hypothesis that lobar pneumonia is primarily a septicemia with secondary localization of the inflammatory process in the lungs. The work of Stillman and Branch with mice indicates that septicemia may develop from

intrapulmonic implantation and further, that certain factors of resistance may determine the localization of the inflammation in the lung.

Experimental investigation shows that in animals the earlier lesions arise near the hilus of the lung and thence spread to involve the entire lobe. There can be no doubt that in experimental animals interstitial and lymphatic involvement is somewhat more prominent than in man. The early phases of pneumonia in man progress so rapidly and the difficulty of obtaining material at this time is so great, that it has been impossible to confirm a definite similarity between these early stages in man and the early stages in animals. In animals the lymph nodes show the effects of lymphatic involvement earlier than do the lymphatic vessels and this cannot be said to be true of man. On the other hand, there is no good reason for believing that in man essentially the same process may not occur, namely, involvement primarily near the hilus of the lung and then a spread to involve an entire lobe. Many theoretical explanations have been offered for the confinement of the process to fairly restricted areas, but if it be accepted that spread comes by way of lymphatics, it is easy to understand how a single lobe may be involved. The same, of course, is true in regard to extension to neighboring parts of adjacent lobes. Similarly, the involvement of the pleura in the acute fibrinous inflammation may be explained by extension through the pleural lymphatics. Although the natural drainage of the lymphatic system is toward the hilus of the lung, this does not exclude the extension of the inflammatory process in the reverse direction. Blake and Cecil regard pneumonia as primarily an interstitial infection of the lung, and Permar is of the opinion that the process is comparable in its essentials to that taking part in the pneumonias of man, thus supporting the theory of lymphatic distribution.

Cotoni and his collaborators support the hypothesis of Fernet that the localization of the pneumonia is a sort of herpetic manifestation, possibly dependent upon lesion of nerve groups or ganglia with consequent vascular disturbance in the area supplied by these nerves. In this disturbed area the inflammation develops. In our opinion, this view is not adequately supported. A further hypothesis worthy of note is that the predisposing causes may induce a pulmonary edema, thus converting the separate lobes into a sort of flask containing fluid nutrient for bacteria. Aspiration of pneumococci into a lobe would lead to rapid growth within the fluid in that lobe and thus constitute a lobar involvement.

Cells of the Exudate.—In the early stages the mononuclear cells play an important part in the exudate. The lymphocyte and polymorphonuclear leucocytes can be identified readily. The large mononuclear cells are in part epithelial cells from the lining of the bronchioles, infundibula and alveoli. There are in addition mononuclear phagocytes capable of ingesting cell fragments and other detritus. Although they may come in small part from remote organs such as spleen and omentum, it appears that the majority originate in the blood vessels and lymphatics of the lung. Evans was of the opinion that certain of the large mononuclear cells are the so-called transitional

cells of the blood. The more recent studies of endothelial reactions, however, and especially the use of the oxidase test in identifying the cells, throw some doubt upon this assumption. Certainly, such transitional cells are of little significance as compared with the large mononuclear endothelial phagocytes.

Resolution.—When the disease has progressed for some time, as a rule seven to eleven days, the exudate usually but not constantly begins to dissolve. This is quite independent of whether clinically there is crisis or lysis of the disease. Solution occurs in the exudate because of ferments and does not affect the living tissues which, as elsewhere, are resistant to ferment action. The observation by Flexner of ferment action has been studied extensively by Opie, Kline and Winternitz, Kline, Jobling, Petersen and Eggstein and others. The exudate in the consolidated lung shows increased hydrogen ion concentration (Lord) and contains the products of protein disintegration including a variety of amino-acids, thus showing that protein breakdown has occurred. Lord has shown that from the cells there is liberated a proteolytic enzyme capable of digesting coagulated protein and probably also capable of splitting peptone to amino-acid nitrogen, the latter activity operating over a wider range of pH concentration than the former. Avery and Cullen demonstrate ferments in pneumococci, which act as protease, peptonase, lipase, invertase, amylase and inulase. The quantitative relation between the ferments of the exudate and those of the pneumococci is not determined, but it seems probable that those of the exudate are of more importance. Increasing acidity of the exudate may limit the activity of the proteolytic ferments but also to be considered is the presence of antiferment in the blood. With solid exudate the access of plasma is probably restricted and if, as Kline and Winternitz maintain, the circulation through the consolidated lung be diminished, there is additional reason for decreased supply of antiferment and accordingly more free activity of the ferments. Although the question is not finally settled, the fact that hydrogen ion concentration is greater in the pneumonic lung than in other tissues points toward poor circulation. Kline believes that intratracheal injection of serum delays resolution, further indicating that resolution is favored by decreased access of antiferment. Lord and Nye find that at pH 6.8 to 5.1 the pneumococcus is rapidly killed and is injured at pH 6.8 to 7.4. The increased acidity of the consolidated lung is in part due to growth of the pneumococci, which here as in culture, build up an acidity which is fatal to the organism. In addition to immune processes in the body the chemical character of the exudate thus favors limitation of the disease.

Physiology.—It is well known that in pneumonia the blood pressure is diminished and venous distention may be prominent. When the heart dilates the enlargement is more noticeable upon the right side. The latter probably has to do with mechanical interference with circulation through the pulmonary vessels. Newburgh and Porter, on the basis of experiments with dogs, are of the opinion that the heart muscle is not intrinsically damaged by pneumonia, but that its decrease in working capacity is due to lack of proper food in the blood. Owing to a doubt that the lobar pneumonia of dogs is identical with that of

man, and also to the fact the dog's heart is that of a running animal and therefore probably endowed with greater reserve than that of man, we do not believe that these conclusions are directly applicable to man. Furthermore, anatomical studies usually show cloudy swelling of a heart that has failed during the course of pneumonia. Unless the consolidation be extremely extensive or complicated by edema the carbon dioxide content of the blood is usually low. There is, however, considerable difference of opinion and perhaps of observation concerning the oxygen content of the blood, but it appears to be true that certain cases show a decreased oxygen content and can be benefited by the administration of oxygen in the respired air (Lundsgaard). In these cases, it seems probable that the fault is not directly connected with the oxygen combining power of the blood. On the other hand, Butterfield and Peabody have shown that the pneumococcus may produce methemoglobin in the blood, but ordinarily the acid content of the blood is not sufficiently high to permit of this being a serious factor. Where it is demonstrable it is usually of bad prognostic significance. Peabody finds that not only is there a retention of chlorine in the body but also of sodium and calcium; this, however, is not true of potassium and magnesium. The output of ammonia may be high. Palmer shows that the output of organic acids is similarly high, but except in most severe cases there is little disposition to acid intoxication (see also Hastings et al.).

Immunity.—The great susceptibility of races and groups not commonly exposed to pneumonia, when brought in contact with the disease, makes it probable that the survival of the disease by several generations leads to a group resistance. This, however, is not true in the individual. Osler states that recurrences are observed in about 27 per cent. of the cases and that certain persons show many recurrences. Cecil and Blake suggest that recurrences are due to other fixed types or members of type IV than that of the original attack, but this view is opposed by Friedberger and by Vaughan and Wheeler. Although immune bodies are developed in man, actual immunity is not lasting. Clark and Murphy find that the failure of immunity is not due to the location of the organisms in the consolidated lung, except perhaps in degree, but rather to the poor antigenic character of the pneumococci. In our opinion the work of Cecil and Austin indicates that immunity may be conferred upon man by vaccination. In the hands of Cecil, Steffan and Perlzweig, vaccination also confers protection upon monkeys, specific in the case of type I pneumococcus but not necessarily so in the other types. A definite toxin has not yet been isolated and the therapeutic immune sera are to be regarded as antibacterial rather than antitoxic. Certain workers have found the use of type I anti-pneumococcus serum of considerable value therapeutically, although the results are not so striking as with certain other immune sera. Agglutinins, precipitins, and complement fixing bodies are relatively readily produced in experimental animals. Bull has demonstrated that immune animals agglutinate and phagocytose pneumococci more readily than do non-immunes. Cutaneous reactions have not been satisfactorily demonstrated.

Complications.—Pneumonia being a general infectious disease, it is to be expected that cloudy swelling and even fatty degeneration of the parenchymatous viscera may occur. *Pneumococcus septicemias* complicate only the more severe cases and are to be regarded as of serious prognostic significance. In these cases endocarditis may occur (see Locke). According to the work of Peabody, the septicemic cases are those in which methemoglobin formation is more likely to be observed. The simpler cloudy swelling of the kidney may progress and become an acute nephritis. Of great importance is the transformation of a simple fibrinous or fibrinoserous pleurisy into empyema. Extension of the pleural inflammation may involve the pericardium and the upper parts of the peritoneum. *Pneumococcus meningitis* may be a complication or sequel of pneumonia or may occur independently. An excellent review of the complications is given by Berry.

The complications within the lung itself include especially organization of the exudate, gangrene, and abscess formation. Organization of a small part of the exudate is not uncommon but only rarely does organization become co-extensive with the original pneumonic process. If the process of resolution depend upon the activity of ferment, it can be understood that the presence of considerable amounts of antiferment may so interfere with solution of the exudate as finally to result in organization. Kline finds that insufflation of serum into the pneumonic lung tends to lead to organization and it seems probable that the restoration of circulation, after the exudate has somewhat softened, may prevent further softening and thus favor organization. New blood vessels and connective tissue grow into the exudate from the alveolar wall. The movement of the growing fibroblasts is apparently directed, to a certain extent, by the fibrin of the exudate. Thus, the lines of organization are likely to radiate out from the general situation of the pores of Cohn and parallel the lines of fibrin in the exudate.

The production of abscess depends upon invasion by pyogenic organisms, such as *staphylococcus* or *streptococcus*. Such abscesses may be single or multiple, usually the former, and are not so extensive as the original consolidation, usually being much smaller. Both grossly and histologically, the abscess is characterized by pus formation, which leads to extensive destruction of pulmonary tissue. It is a serious and usually fatal complication, although by postural and surgical treatment cures have been reported.

Gangrene presupposes the occurrence of some necrosis in the course of the disease and subsequent to this the invasion of saprophytic organisms. The investigations of Kline indicate that pulmonary gangrene is commonly due to the activity of fusiform bacilli and spirochetes similar to those of Vincent's angina, usually associated with a considerable number of other organisms. Gangrene may lead to rapid death or may become subchronic in course, resembling somewhat tuberculosis of the lungs. Neither abscess nor gangrene necessarily depends upon preëxisting pneumonia, as they may occur independently of this process. Abscess for example, may be induced in the lung by lodgment of infected emboli. It may also result from aspiration of

food and other particles which lodge in remote parts of the bronchial tree and lead at first to a local pneumonia which rapidly becomes suppurative. Abscesses of either of these types are likely to be multiple. Gangrene may appear on the basis of tuberculosis, tumors, and sometimes arises without any determinable preëxisting cause. Depending upon situation, as to whether it is near the pleura or not, course of the disease, and cause of the disease, both abscess and gangrene may be complicated by pleurisy which, in the earlier and less



FIG. 248—Multiple abscesses of lungs, due to streptococcus hemolyticus. Army Medical Museum 1141.

severe cases may be a simple acute fibrinous pleurisy or may become suppurative. In the chronic cases of gangrene, chronic adhesive pleurisy is likely to be found. The gross appearance of gangrene and of abscess may at times be somewhat confusing, but practically always the foul odor and the brown or green necrotic tissue of gangrene are sufficient for the diagnosis. The odor also aids in the clinical differentiation of these diseases. Microscopically, both processes show extensive destruction of lung substance, surrounded by reactive inflammation. In the abscess, however, the suppurative character of the reaction is more pronounced and the exudate much richer in polymor-

phonuclear leucocytes. Further complications of these two processes are essentially the same in the lung as when they occur in other situations.

Bronchopneumonia.—In its narrowest sense, this term is applied to those forms of pneumonia which extend from a bronchitis so as to involve small portions of the lungs immediately adjacent to a bronchiole. The pneumonic process, therefore, is likely to be lobular in character. In its broadest sense, the term is commonly employed to cover all forms of pneumonia not suppurative and not lobar in character. It is not a specific disease as is lobar pneumonia but may be caused by a wide variety of agents, either infectious or simply irritative. In the commoner infective forms the general symptoms of infectious disease accompany the inflammation. The same complex of general symptoms may, but does not necessarily, accompany the irritative forms. The causative organisms include a wide variety such as staphylococcus, streptococcus, pneumococcus, Friedländer's bacillus, other mouth organisms, colon bacillus, and others which may cause infection in any situation. On the other hand, the process may be more or less specific, as is seen in pneumonic plague. With the exception of certain special forms of bronchopneumonia to be mentioned subsequently, the disease appears to attack the extremes of life, namely infancy, childhood and old age, but is not especially more common in males than females and shows no particular racial predisposition. Failure of circulation predisposes to that especial form known as hypostatic bronchopneumonia. The disease is often preceded by a more or less prolonged bronchitis, and as a rule the same organism which causes the bronchitis causes the bronchopneumonia. It complicates a number of acute infectious diseases such as measles, pertussis, influenza, diphtheria and less frequently scarlet fever and other infections. It may also result from irritating gases such as chlorine, ammonia, nitrogen tetroxide (Wood), bromine and certain of the war gases, particularly that known as mustard gas. These are sometimes referred to as chemical pneumonias. We have shown that in the rabbit inhalation of oxygen over considerable periods of time will lead to bronchopneumonia. Lobular types of pneumonia may also accompany septicemia, in which case the organisms are brought to the lung by the blood stream, thus causing exudation into the alveoli without necessarily involving the bronchioles.

The commoner types of bronchopneumonia show patchy areas of consolidation, particularly in the lower lobes of the lung, usually bilateral and sometimes extending widely throughout all the lobes. Sometimes the patches are coextensive with physiological or anatomical lobules, but as a rule this distinction cannot be made out and the areas are irregularly distributed, usually rather poorly defined, varying in diameter from 5 to 15 mm. or more, and associated with general pulmonary hyperemia frequently accompanied by edema. The bronchioles and usually the bronchi are the seat of an acute catarrhal inflammation, the exudate of which may be distinctly purulent in character. The nodules of consolidation are easily palpable in the unopened lungs and in the cut surface project slightly as firm, moist lobules from which the exudate may readily be expressed as slimy or mucopurulent or distinctly

purulent drops. Even in those instances where fibrin appears in the exudate the cut surface is not so dry as in lobar pneumonia. In the earlier stages the patches are pink or red whereas in the later stages they become yellow or gray in color. Acute fibrinous pleurisy is not constant but may be observed more especially in those cases where the consolidation approximates the pleura. Empyema may also accompany bronchopneumonia, apparently more commonly in those cases due to the streptococcus hemolyticus than to other organisms. Acute fibrinous pleurisy is frequent in mustard gas pneumonias but not so common in other irritative forms. It is not rare for areas of bronchopneumonia to become confluent so that they occupy a considerable portion

of or an entire lobe. The gross confusion with lobar pneumonia is usually obviated by noting the moist non-granular character of the cut surface, and the fact that in adjacent lobes and in other lobes there are patches of bronchopneumonia rather than the extension of lobar pneumonia. Microscopically, the exudate is usually seen to be patchy in character involving smaller or larger groups of alveoli, although in the confluent forms this cannot be made out. Hyperemia is likely to be prominent. The bronchi and bronchioles show catarrhal inflammation with desquamation of epithelium, and catarrhal exudate within the lumen. In the more severe and long standing cases, exudation of polymorphonuclear leucocytes is found in the bronchiolar and bronchial walls and the exudate within the lumen is distinctly purulent. Within the alveoli the earlier and simpler stages show principally lymphoid cells, desquamated epithelium and endothelial cells, the last

identified by phagocytic properties. Leucocytes appear in small numbers. This differs from the early stage of lobar pneumonia principally in distribution and in the more widespread affection of bronchi. In addition, fibrin does not appear so early or in such great quantities, and in many bronchopneumonias it is entirely absent. Whereas in lobar pneumonia, edema is practically constant in the early stages, in bronchopneumonia it may be absent. In bronchopneumonias due to pneumococcus and diphtheria bacillus, fibrin may be fairly conspicuous, and in the latter condition involves not only the alveoli but frequently also the peribronchial and perivascular lymphatic spaces. In the later stages of bronchopneumonia, polymorphonuclear leucocytes appear in greater and greater numbers but rarely entirely blot out the mononuclear cells. The lung

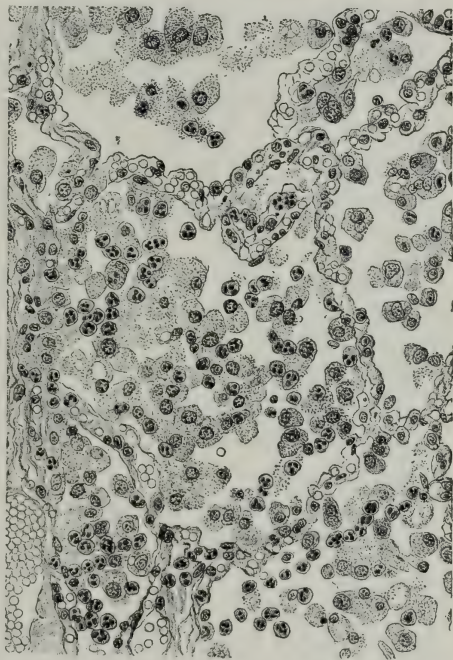


FIG. 249.—Early bronchopneumonia in which most of the cells are desquamated alveolar epithelium.

intervenning between the consolidated areas may show nothing other than hyperemia or may show edema with a moderate amount of desquamation of lining cells. In the early stages of bronchopneumonia the associated bacteria are richer in the bronchioles than in the alveoli, but as the process extends they are found in great numbers in the alveoli. In certain cases, more especially the pneumonic form of plague and also in streptococcus hemolyticus pneumonias, hemorrhage is a prominent feature both grossly and microscopically. With recovery the exudate undergoes resolution in essentially the same way as in lobar pneumonia. In bronchopneumonias also there may be organization of the exudate and the disease may be complicated by the occurrence of abscess or gangrene.

The primary bronchitis and bronchiolitis may extend into the alveoli either by continuity along the epithelial surface, or by contiguity through the bronchial walls and interstitial tissues, to neighboring alveoli. In the former the involvement is principally in the physiological lobules, whereas in the latter it is more irregular. It is difficult as a rule, however, to distinguish these processes in any given section, and certainly in the later stages both types of process play a part.

Clinically, bronchopneumonia usually comes on insidiously, frequently following prolonged bronchitis. The period of fastigium or acme is of irregular duration, sometimes being relatively short and sometimes extremely prolonged. Crisis is very unusual, most of the cases tending toward convalescence after a variable period of lysis. This, of course, does not apply to certain special forms of pneumonia and the bronchopneumonia of septicemia.

Hypostatic Bronchopneumonia.—This is a common terminal event in patients who die from a chronic or acute heart disease where there is passive hyperemia in the lung. The passive hyperemia affects particularly the lower and posterior parts of the lung and accordingly the pneumonia is likely to appear there. Passive hyperemia of the lung, as elsewhere, is likely to predispose to catarrhal inflammation which may be directly excited by bacteria of various kinds. Hypostatic pneumonias are usually bilateral but not very extensive. Grossly, the red, hyperemic, edematous, bloody, lower posterior parts of the lung are found to contain easily palpable nodules which in the cut surface are solid, poorly defined, projecting masses, which may be of the same color as the surrounding hyperemic lung or of lighter gray or deeper red color. In the later stages, the color may be gray or yellowish-gray. Sometimes these areas become confluent to form fairly large patches of consolidation. The bronchi are the seat of subacute catarrhal inflammation but the pleura is not often affected. Histologically, the exudate is patchy in distribution and shows involvement of bronchi, bronchioles and alveoli. In both early and later stages there is likely to be a greater amount of edema and diapedesis of red blood corpuscles than in the ordinary bronchopneumonia. In the later stages hematogenous pigmentation may be prominent, which also is true if the preceding hyperemia has been of long duration.

Aspiration Pneumonia.—Many pneumonias are due to aspiration of infectious material from positions higher up in the respiratory tract, but this term is usually applied to those pneumonias where large particles of infectious material are drawn into the bronchi. These include particularly food particles and particles of exudate, especially of pharyngeal diphtheria. The material aspirated passes down through the bronchial tree and lodges in some distal part. The respiratory surface, tributary to the bronchus or bronchiole affected, may show simply atelectasis after the absorption of the contained air but as infective agents are commonly present, and, as Meltzer indicates, closing off of a number of alveoli favors the growth of bacteria, infection extends through a more or less conical area immediately under the pleural surface, establishing a pneumonia which in the earlier stages is similar to other forms of bronchopneumonia save for the peculiar subpleural disposition and the likelihood of subsequent suppuration. Overlying these areas there is an acute fibrinous pleurisy which may become purulent in character. The cut surface shows the generally triangular outline with the base toward the pleura. The triangular area is well defined, elevated above the rest of the cut surface, red in the early stages, and gray and yellow in the later stages. When suppuration ensues it may extend laterally so as to increase the area involved and blot out the triangular shape and the clear definition.

Influenza.—This is a disease more especially of the upper respiratory tract but sometimes shows severe or dominant symptoms in the alimentary canal. In adults it is likely to produce a pneumonia in from 10 to 15 per cent. of cases (Conner). It is observed in endemic, epidemic and pandemic form, the data of which have been well studied by Vaughan. Some support the hypothesis that it is due to bacillus influenzae of Pfeiffer (notably McIntosh). Park denies the etiological relationship of bacillus influenzae. It is present in more than 80 per cent. of patients with the disease but is also present in normal throats. It is found in lymphatics of the lung in early influenzal pneumonia almost to the exclusion of other organisms, but as yet has not satisfactorily produced the disease upon inoculation. We agree with Opie that the data at present available do not justify a definite conclusion as to the relation of Pfeiffer's bacillus to the disease. Gates and Olitsky suggested bacterium pneumosintes, a filter passing organism, as the cause, but as indicated by Nichols this cannot as yet be accepted. Clinically, the disease appears as a general infectious disease with cough, angina, fever, headache and muscle pains, following a short incubation period of rarely more than three days. Low blood pressure is common. Symptoms referable to central nervous system and special senses are not rare. Scarlatinoid and macular eruptions may occur. There may be vomiting and diarrhea. The kidneys show little more than the signs of cloudy swelling. The pneumonia may be further complicated by abscess or empyema. Vaccination is variously reported as valuable and useless; we incline to the latter view. Various immune bodies are reported but apparently complement fixation with bacillus influenzae has given positive results in many cases (Kolmer, McIntosh). This summary is preliminary to the discussion of post-

infectious pneumonias. The pathological anatomy has been well studied by Lucke, Wight and Keim, by Klotz and others. Influenza is not in itself commonly fatal; the high death rate of certain epidemics is due to the complications rather than the disease itself.

Postinfectious Pneumonia.—In diphtheria, pneumonia may develop as the sequence of aspiration of exudate, producing a bronchopneumonia with considerable fibrin in the exudate and sometimes fibrin in the interstitial tissues and lymphatics. The predominating organism under these circumstances is the diphtheria bacillus. This does not exclude, however, the possibility of development of pneumonia in diphtheria, nasal, pharyngeal or laryngeal, due to other organisms. In such instances the character of the exudate depends to a certain extent upon the organism involved, except that pneumococcus bronchopneumonias may or may not show fibrin formation. In pneumonias following whooping cough, measles, and influenza the pneumonic process is practically always due to organisms which must be regarded as secondary invaders. In pertussis, the pneumonia may be caused by the staphylococcus and run a comparatively mild course, but in certain instances the disease may be severe and fatal. Finding the Gengou bacilli in the cilia of the bronchial or tracheal epithelium, as described by Mallory, may serve to identify this type of disease. In measles, the severity is somewhat greater and in influenza, the pneumonias are fatal in a considerable proportion of cases. Much of the information which we now have concerning pneumonia following measles and influenza has been the result of studies conducted during the Great War. In this country admirable work was contributed by various commissions appointed by the Army to study these epidemic diseases. Perhaps the most extensive publications on this subject are those by the commissions headed by MacCallum and by Opie. The character of the pneumonia varies considerably but is not essentially different as regards the two primary diseases. The outstanding organism concerned was the streptococcus hemolyticus, although the pneumococcus and staphylococcus played important roles. In our experience this type of disease showed more commonly than is otherwise observed a combination of lobar pneumonia and bronchopneumonia. There is a striking tendency to interstitial and intra-alveolar hemorrhage as well as to acute emphysema. Many cases show as a dominant feature of the pathological picture, the so-called acute interstitial pneumonia in which the exudate, made up principally of leucocytes, accumulates in perivascular and peribronchial situations forming nodules which to the naked eye are two to three millimeters in diameter, white or pale yellow in color, projecting above the cut surface of the lung, sometimes with a fine central depression representing the small bronchus or bronchiole. Without careful examination the picture may be confused grossly with that of miliary tuberculosis. Wolbach is of the opinion that in influenzal pneumonias the frequent occurrence of bacillus influenzae is of great significance, as pointing toward it as the probable cause of the earlier manifestations of pneumonic disease. He finds that the early change is an acute alveolar emphysema in which the alveoli are lined by

hyaline fibrin. Between these areas of emphysema there may be various types of consolidation, and as secondary invaders, such as streptococcus or pneumococcus, manifest their activities, the character of the pneumonia may materially change, thus producing various types of discrete or confluent bronchopneumonia, interstitial pneumonia and even lobar pneumonia. In his series of influenzal pneumonias this feature was constant. Others, including MacCallum, have expressed the view that although this may be constant in influenzal pneumonias, nevertheless, it is frequent in other postinfectious pneumonias, notably those following measles. It cannot therefore be regarded as pathognomonic of postinfluenzal pneumonia. We believe the acute emphysema to be due to cough accompanying the bronchitis or general infectious disease which precedes consolidation. Indeed, the swelling of the lining of the bronchioles and the accumulation of exudate may be sufficient to obstruct and lead to areas of atelectasis, which are common in all postinfectious pneumonias and particularly notable in any of the bronchopneumonias of childhood. In MacCallum's experience the acute interstitial pneumonia is most likely to be associated with streptococcus hemolyticus. He points out further that pneumonias similar to those seen following measles and influenza may arise without these diseases as preliminaries and spread in infectious form.

In some of the postinfectious pneumonias the disease may be considerably prolonged and in these instances the epithelial cells of alveoli may fuse to form giant cells (Karsner and Meyers).

In these later stages the exudate is not so severe or active as in the earlier stages and the giant cells may dominate the picture giving the name giant cell pneumonia. This, however, is not a special form of bronchopneumonia; it simply represents one of the later stages. Similar giant cell formation is sometimes found in those pneumonias due to irritant gases (Wood).

Acute Interstitial Pneumonia.—In the preceding section it is pointed out that acute interstitial pneumonia may occur in postinfectious pneumonias. Nevertheless, acute interstitial pneumonia may arise otherwise than as the sequence of acute infectious diseases. It may extend from suppurative lesions of neighboring structures such as the pleura, mediastinal lymph nodes, tissues of the neck and the vertebræ. In these latter instances, the process extends along peribronchial and perivascular lymphatics and interalveolar tissues,



FIG. 250—Bronchopneumonia, acute interstitial pneumonia and acute emphysema in influenza pneumonia. Army Medical Museum 3130.

forming long and somewhat branching, more or less purulent, white or yellowish-white lines two or three millimeters or more in diameter. These may extend inward from the pleura constituting the so-called pleurogenous pneumonia, or may extend outward from the hilus of the lung. In the postinfectious form, the lines are not so continuous and are more likely to be observed



FIG. 251—Acute interstitial pneumonia showing peribronchovascular distribution and central depression of minute bronchi.

in cross section where they constitute slightly projecting white or yellowish-white masses, sometimes showing the central depression of a bronchiole from which pus may be expressed. In either case the surrounding alveoli are likely to be involved by the inflammatory process. The bronchi are also involved in the inflammation and may be more or less occluded by swelling and exudate, thus leading to areas of atelectasis. The acute interstitial pneumonia of infectious diseases was described by Delafield, whose beautiful description has been elaborated more especially in this country by MacCallum and by numerous workers abroad. The inflammation of the bronchioles may be so extensive as to constitute the so-called bronchiolitis obliterans, which by organization of the exudate may become permanent. The lymphatics contain exudate made up principally of leucocytes, associated with variable amounts of fibrin and

with other cells. The involvement of the alveoli is especially by contiguity. They are usually airless and contain leucocytic and fibrinous exudate. In those forms resulting from extension of suppurative processes in the neighborhood, true suppuration in the bronchi, in the peribronchovascular lymphatics and in the alveoli is more likely to occur than in the postinfectious forms.

Chronic Interstitial Pneumonia.—Sometimes included under this heading are various reparative processes which lead to the cicatrization of infarcts,

abscesses, gangrene, tuberculous foci including conglomerate tubercles or cavities, and wounds of various kinds. The organization of lobar or bronchopneumonia is sometimes referred to as a chronic interstitial form. It is deemed preferable, however, to refer to these as cicatrization since they are not likely to be progressive except in the case of tuberculosis. A progressive fibrosis of the finer connective tissue between the alveoli and around the bronchioles is observed particularly well in chronic passive hyperemia. This is likely to be

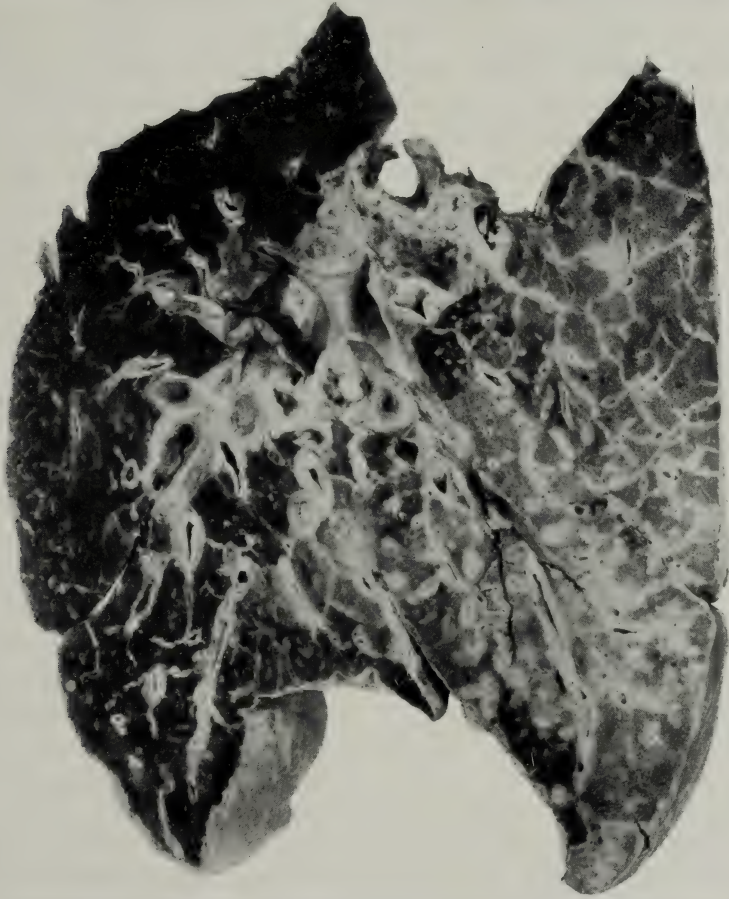


FIG. 252—Acute interstitial pneumonia with many areas cut in longitudinal section. Army Medical Museum 606.

progressive as long as the passive hyperemia exists, and is well exemplified in the so-called carnification of the lung associated with mitral stenosis. The gross manifestation of the chronic induration is found in increased density of the lung and increased resistance to cutting. Also involving the finer parts of the connective tissue, but likely to be present in fairly large foci, is that progressive fibrosis of the lung which is seen in connection with various forms of pneumokoniosis. In more extensive cases of fibrosis of the finer connective tissue shrinkage may occur so as to reduce the total bulk of the lung. Involvement of the larger connective tissue septa so as to produce dense, fairly thick,

interlacing lines of fibrosis through the lung may be seen in connection with chronic fibrous pleurisy, from which it extends usually only a short distance but may involve the entire lung. Somewhat more common is fibrosis of denser parts of the supporting connective tissue, radiating out from foci of chronic tuberculosis, more especially in those cases where cavities have formed and secondary infection with other organisms produces a prolonged irritation. A similar degree of fibrosis may be non-tuberculous (Atkinson). The dense fibrous connective tissue may be white or grayish-white or may show foci of deep anthracotic pigmentation. Histologically, the character is simply that of dense old connective tissue. Shrinkage of the lung or the part of the lung involved is more common in those cases where the fibrosis involves larger septa than in those where the finer connective tissue is affected.

Infectious Granulomata.—Many of the infectious granulomata may involve the lung, but in adult life the one of outstanding importance is tuberculosis. Actinomycosis, glanders and syphilis may also affect the adult lung. Syphilis, however, is of considerably more importance in the fetal lung than in the adult lung. Our discussion of the granulomata will be more specifically directed toward tuberculosis and syphilis than the other granulomata.

Tuberculosis.—The modes of entry of the tubercle bacillus have been discussed in the chapter on infectious granulomata, and in that place the discussion of entrance into the lungs was taken up. Of importance is the view that infection of the lung occurs in early life either by inhalation of tubercle bacilli or implantation into the lung from infected objects. This leads at first to a miliary tubercle in the lung with rapid secondary involvement of the mediastinal lymph nodes, and the remote possibility of retrograde dissemination in the lung from the infected lymph node. As was pointed out, there is some difference of opinion as to whether the tuberculosis of the lungs in adult life represents an extension from the primary infection of childhood, or is entirely independent. In the lung the human form of tubercle bacillus is the one principally, if not solely, concerned. The reaction to tubercle bacilli is in the form of exudation, proliferation or both. The tubercle must be regarded as principally proliferative, although in the earlier stages there must certainly be some exudation. In contrast to this, however, is the other form of involvement of the lung, namely, tuberculous pneumonia which primarily and principally is exudative in character. The determination of reaction on the part of the lung involves question of virulence and dosage of tubercle bacilli as well as sensitization and local or general resistance. The fact that the wax of tubercle bacilli, and other foreign bodies, may produce nodules practically identical with the tubercle, suggests the possibility that the more intense exudative reactions are in response to toxic products of the organism. Nevertheless, in tuberculous pneumonia large numbers of organisms are present, and it may well be that dosage of organism is of equal importance with production of toxic materials.

There are recognized three modes of dissemination within the lung, namely, by the blood stream, by the lymphatic stream, and by the air passages. In

order to simplify the discussion these will be taken up in the order mentioned. It must be noted, however, that the direct local invasion of the tuberculous process is of the greatest significance and probably represents the most frequent form of spreading of the disease.

Miliary Tuberculosis.—Miliary tuberculosis of the lungs is a blood borne disease. Penetration of a focus within the lung or mediastinal lymph nodes into a pulmonary artery may lead to dissemination either within the same lobe, several lobes or throughout both lungs. As a rule, the process is acute. The lungs are enlarged and hyperemic. There may be a miliary tuberculosis of the pleura, an acute exudative tuberculous pleurisy, or tubercles may simply be visible under the pleura through an otherwise normal membrane. Palpation discloses innumerable fine nodules. The cut surface shows these

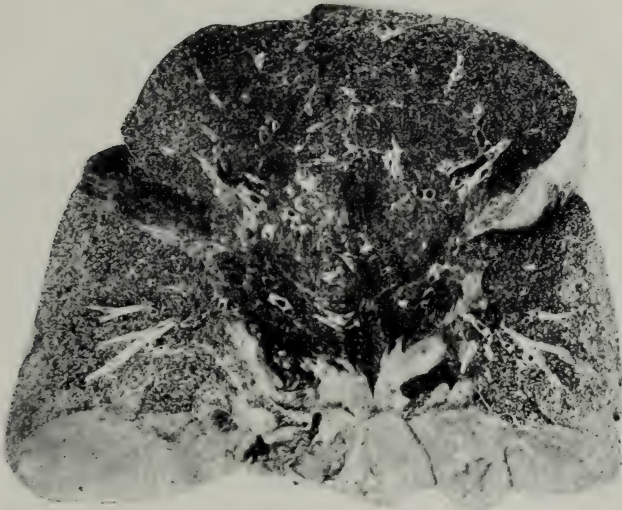


FIG. 253—Acute miliary tuberculosis of lung. Army Medical Museum 2779.

nodules approximately of the same size, distributed widely and usually uniformly throughout. They are discrete, gray or pale yellow, well defined, projecting spherical nodules, 1, 2 or 3 mm. in diameter. The process may be confined to the lung but is commonly associated with a similar condition in other viscera, particularly the liver, spleen and kidney. Emphysema is occasionally found but usually is absent. Histologically, the nodules may be single miliary tubercles, with the usual histological character of centrally disposed endothelial cells surrounded by lymphoid cells, and frequently fairly numerous Langhans giant cells. More common, however, is the finding that the tubercles which grossly appear as discrete single masses are histologically made up of fusion of one, two, three or more true miliary tubercles. In either case, caseation may be present but is likely to be more prominent in the latter. Hyperemia is usually prominent. The tubercles of course, are interstitial in situation but apparently have no predilection for a site near the bronchioles or

smaller blood vessels. Whether the tubercles originate within a capillary where the bacilli are deposited, or whether the bacilli migrate or are carried either into neighboring lymphatics or into the alveolar spaces is not definitely known. Reaction in the surrounding alveoli is limited in amount, but occasionally slight desquamation and infiltration of lymphocytes and even polymorphonuclears may be observed. Bronchitis is not a prominent factor.

If the patient survive a sufficient length of time the miliary tuberculosis may become chronic in character. Grossly, the distribution is the same but hyperemia is likely to be less marked. The nodules are commonly somewhat larger than in the acute form, sharply circumscribed and firm. Histologically, they are characterized by distinct connective tissue formation in the margins, which may be loose masses of fibroblasts, or thin but dense connective tissue capsules. Anatomically, the quantitative destruction of alveoli does not appear to be extensive but clinically, reduction of vital capacity is often a very striking phenomenon. This may be due in part to the tuberculosis, and contributed to by the hyperemia which is common in the acute form.

Lymphogenous Tuberculosis.—The extension of tuberculosis in the adult lung through the lymphatic tracts cannot be regarded as finally established, and indeed many regard the form described under this name as hematogenous in origin. It forms a distinct variety anatomically and tends to be located principally in perivascular and peribronchial lymphatics. This may, however, be due to interstitial deposition of organisms from the vascular tree and subsequent extension into the neighboring lymphatics. If it extend in the lymphatics, it must progress against the stream, and the proponents of this hypothesis suggest that with occlusion of the lymph nodes at the hilus by tuberculosis, a retrograde flow toward the periphery is established. The peribronchial and perivascular lesions may be confined to a lobe or involve several lobes. Usually there is a preëxistent tuberculosis, either chronic ulcerative, or conglomerate caseous in the lung, or massive tuberculosis of the hilic lymph nodes. Cross section of the lung shows that what seem to be nodules a centimeter or more in diameter upon external palpation, are made up of staphyloid clumps of tubercles, each tubercle being about 1, 2 or 3 mm. in diameter. The individual members of the group are fairly well defined, projecting, gray or yellowish-gray masses, which upon close inspection reveal a minute point of central depression, corresponding to a small blood vessel or bronchiole. The masses of tubercles are commonly found in the center of the lung rather than near the periphery. Microscopically, they are fused miliary tubercles in the perivascular or peribronchial lymphatics. Neighboring hyperemia is prominent and indeed, alveoli in the immediate neighborhood may show the exudate of tuberculous pneumonia. The walls of the bronchi may be infiltrated and tubercles appear in the lining membrane. The same may be true in regard to the smaller blood vessels. It is unusual for this process to become chronic in character, and therefore it is uncommon to find connective tissue reaction of any significance either grossly or microscopically. This peribronchial or perivascular tuberculosis represents an extremely common form of extension of

the disease in association with chronic ulcerative tuberculosis of the lung. It must not be confused with tuberculous pneumonia whose picture is distinctive.

Aërogenous Tuberculosis.—Under this heading must be included that form of tuberculosis which is common in the adult, namely, conglomerate tuberculosis in the apex of the lung followed either by cicatrization and calcification or by extension and cavity formation (see Gekler). In addition must be included those forms in which tuberculosis is disseminated from a pre-existing focus, by aspiration of tuberculous material, into more remote parts of the bronchial tree. The latter condition is not very common. Quantities of tuberculous material, particularly from a cavity, may be aspirated into a



FIG. 254—Acute miliary and small conglomerate tubercles in lung of a child.

smaller bronchus, and because of an atelectasis in the area supplied, and partly because of the extension of the disease into this area of diminished resistance, there develops a tuberculous focus of conical shape with the base immediately under the pleura. This may be a mass of small conglomerate or discrete miliary tubercles, or may be an area of caseous tuberculous pneumonia. Overlying it there is almost always an acute miliary tuberculosis of the pleura or an acute fibrinous tuberculous pleurisy, and sometimes a chronic adhesive tuberculous pleurisy. In cut section, the conical outline with the base under the pleura is usually characteristic.

The commonest form of pulmonary tuberculosis in the adult is that which runs one of two courses in the apex of the lung. Rather than enter again into the argument which has been discussed in the general pathology of tuberculosis,

we will assume that this is air borne. In early life, the tubercle bacilli gain entrance to the respiratory tract and are probably immediately transported to the lymphatics where the tubercle is formed. This may remain an extremely minute lesion with or without extensive involvement of the peribronchial and mediastinal lymph nodes, or may grow to form a conglomerate tubercle several millimeters to a centimeter or more in diameter. This may stop and remain quiescent but is not likely to become densely encapsulated by fibrous tissue until later in life. As has been pointed out, although it is common in the upper lobe it is likely to be subpleural in character and toward the lower margin of the lobe. In contrast to this, the early lesion of adult tuberculosis is near the apex but apparently begins and follows the same histogenetic course. Whether it represent a new infection, or is a lymph borne, blood borne or perhaps air borne infection from the childhood focus is still questionable. Why the apex, and more particularly the right apex is selected is unknown. If the limited excursion of the upper part of the thorax has any influence, the same influence should be found in other infections. If the light specific gravity of the tubercle bacillus is of any significance, both apices should be infected with equal frequency, and such a hypothesis assumes that the infection is blood borne. That circulation is less in the upper lobe and therefore resistance diminished has yet to be proven. The fact that the main bronchus to the right upper lobe comes off fairly directly from the trachea might explain lodgment in the right upper lobe but does not satisfactorily explain lodgment in the apex. It may safely be assumed that gaining access to the apex the growth of the tubercle follows the usual course, namely, primary involvement of the lymphatics with the development of a tubercle which, with the multiplication of the organisms, increases in size, both by direct growth and the formation of daughter tubercles, and subsequently a conglomerate tubercle of moderate size is formed. In favorable cases the reaction of connective tissue is sufficiently great to provide a capsule of fibrous tissue around the tubercle and thus limit its growth. As has been pointed out in the section on calcification, the caseous mass within the center of the tubercle is a favorite site for calcification. Thus, these so-called healed tubercles may show either a caseous center or a completely calcified center. Histologically, in these later stages, little that is characteristic of the tubercle remains; there is simply the caseous or calcified center surrounded by dense connective tissue. In the more recent cases, however, the inner layers of the capsule may show lymphoid infiltration. Such healed tubercles, however, are not functionally healed because tubercle bacilli may be recovered by inoculation into animals, although rarely found by histological methods within the mass. Furthermore, instances are found in which new miliary tubercles occur in the neighborhood of the supposedly healed mass, indicating that direct dissemination may occur.

In the less favorable cases the tubercle continues to grow with only a moderate amount of capsule formation and, at any time, hematogenous or lymphogenous or even aërogenous dissemination may occur to other parts of the lung. These accidents, however, are not common until the local process

has become so extensive that it invades a bronchus and discharges its contents into this bronchus to be coughed up and expectorated. This leaves a tuberculous cavity communicating with a member of the bronchial tree. The rich bacterial content of the upper respiratory tract may thus infect the cavity, producing secondary infection. The organisms of secondary infection include particularly the staphylococcus and micrococcus tetragenus, although the

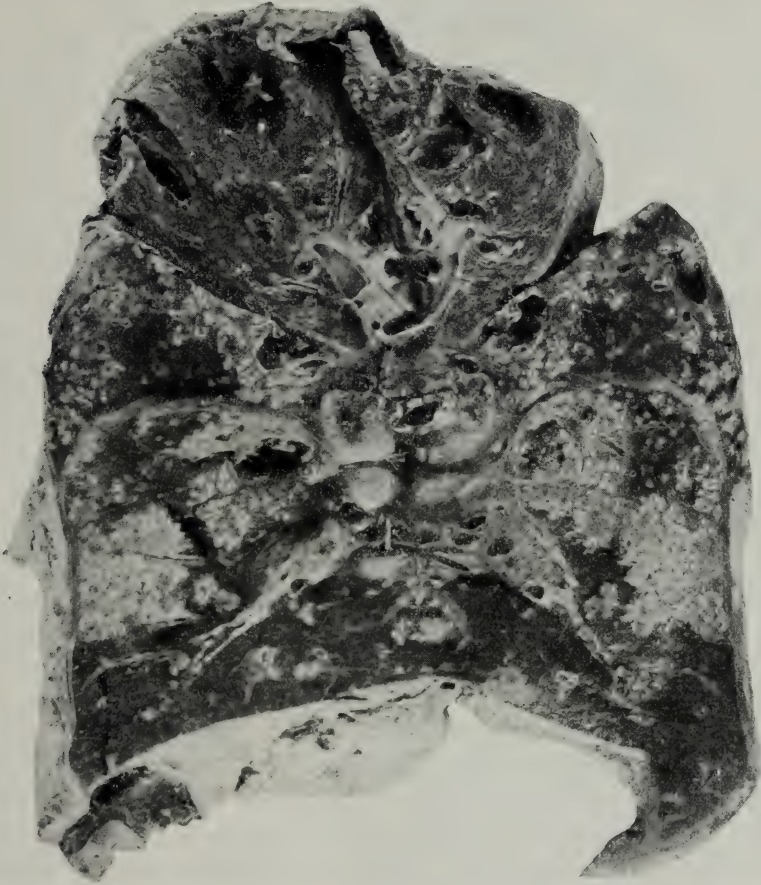


FIG. 255—Chronic ulcerative tuberculosis of upper lobe showing trabeculation and ramifications. Small chronic cavities in middle and upper part of lower lobes. Peribronchial and perivascular tuberculosis of middle and lower lobes. Tuberculous acute fibrinous pleurisy. Conglomerate tuberculosis of peribronchial lymph nodes.

streptococcus, pneumococcus, pneumobacillus of Friedländer and even various forms of yeasts may contaminate the cavity. As the local process extends, there occurs in the bronchi within the lesion a chronic obliterative bronchitis and in the blood vessels a protective thrombosis, with subsequent organization. These constitute fairly resistant dense masses of connective tissue, not readily susceptible to the destructive action of the tubercle bacillus, and they consequently remain as trabeculae or spurs within the cavity. After the secondary infection the cavity may continue to enlarge considerably, but

apparently with the secondary infection the growth of connective tissue becomes more rapid and the fibrosis of the wall of the cavity more extensive. Thus is constituted the cavity of chronic ulcerative tuberculosis. Grossly, the cavity may vary considerably in size from a diameter of 1 or 2 cm. to a size coextensive with the entire upper lobe. It may be generally spherical or may ramify irregularly through various planes in the lobe. The wall is fairly well outlined and under the pleura may be coextensive with the connective tissue of that organ. In most cases the surrounding lung substance is likely to show various forms of tuberculous pneumonia, peribronchial and perivascular tuberculosis and numerous small conglomerate or miliary tubercles. When the lesion is sufficiently near the surface so that the pleura constitutes part of the wall of the cavity, the pleura is markedly thickened by fibrous and often hyalinized connective tissue, and shows chronic fibrous adhesions with obliteration of that part of the pleural cavity. In more deeply situated cavities the pleura may not be involved or may show acute fibrinous pleurisy, miliary tuberculosis of the pleura or a chronic fibrous pleurisy. The thickness of the cavity wall varies from a millimeter to several millimeters and is made up of dense fibrous connective tissue, which may show hematogenous pigmentation and commonly shows a considerable accumulation of anthracotic pigment. The inner surface of the wall is usually rough and irregular because of the persistence of connective tissue septa and the trabeculae formed by obliterated blood vessels and bronchi. The latter may extend through the cavity as dense heavy bands suggesting the stalactites and stalagmites of underground caves. The color of the lining may be dark red, because of granulation tissue; yellow, because of the presence of pus; or gray because of caseation. The contents may be cheesy or caseous or purulent in character, not uncommonly mixed with variable amounts of blood. Sometimes the presence of saprophytic organisms gives a foul odor. The associated tuberculous pneumonias, localized miliary or conglomerate tubercles, peribronchial tuberculosis or other similar processes, may be confined to the upper lobe but as a rule extend to greater or lesser degree into the other lobes. Although the cavity may be in one lung only, the various forms of extension may be observed in both lungs. Histologically, the wall of the cavity is made up of dense connective tissue which may show varying degrees of hyalinization. The surrounding lung shows histologically the same process as indicated above. The inner layers of the wall usually show granulation tissue associated with varying degrees of infiltration of polymorphonuclear leucocytes, depending upon the severity of the secondary infections. In the milder forms of infection, lymphoid cells and endothelial cells may be prominent. It is rare to find actual tubercle formation within the connective tissue of the cavity wall. The process is identified particularly by finding tubercles or other tuberculous processes in the immediate neighborhood. The inner layers toward the cavity may or may not contain considerable numbers of tubercle bacilli. The contents of the cavity, however, are usually fairly rich in tubercle bacilli.

The fibrosis of the cavity wall may apparently be the starting point of a

diffuse fibrosis of the neighboring tissue, wherein dense bands of connective tissue radiate throughout the lobe, or extend more widely in the lung. Sometimes chronic miliary or small conglomerate tubercles are associated with the process. The condition is slowly progressive in character and constitutes chronic fibrous (or fibroid) tuberculosis, more common in late middle than in earlier life. Histologically, there are found heavy bands of fibrous tissue, often with finer fibrosis of alveolar walls and not infrequently showing more or less fibrosed miliary and small conglomerate tubercles. There is destruction of alveolar substance in the progress of the disease. Often there are found small spaces approximating the size of an alveolus lined by cuboidal epithelium. Whether these are old alveoli with pseudo-metaplasia of the lining epithelium or new spaces budding from bronchioles in an attempt at regeneration is not known.

In association with chronic ulcerative tuberculosis there is almost constantly a chronic catarrhal bronchitis and this may be responsible for areas of emphysema in the lung. More particularly in the neighborhood of the cavity, the bronchitis is definitely tuberculous in character with tubercles in the lining mem-

brane. More rarely, as mentioned in the section on diseases of the bronchi, there may be an extensive caseous tuberculous bronchitis. Within the extending tuberculous process the bronchitis may be catarrhal or tuberculous, but in either case the exudate is likely to fill up the lumen, and granulation tissue grow out from the wall of the bronchus so as to convert the tube into a fibrous cord. The blood vessels are usually thrombosed fairly early and this is followed by organization and cicatrization. On the other hand, the outer



FIG. 256—Chronic ulcerative tuberculosis of upper lobe, extensive caseous pneumonia of lower part of upper lobe and lower lobe, and conglomerate tuberculosis of peribronchial lymph node.

layers of vessel walls may be destroyed by the advancing tuberculosis without protective thrombosis. Aneurysms may or may not form, but in either case the weakened walls may rupture, especially when there is increased pulmonary pressure such as occurs in coughing, followed by severe or fatal hemorrhage. Such vascular lesions are more common in chronic ulcerative tuberculosis, but may also occur in small foci of conglomerate tuberculosis and in areas of tuberculous pneumonia. Frequently repeated small hemorrhages may produce anemia of secondary character. Fatal hemorrhages are likely to occur only in connection with chronic ulcerative tuberculosis. Most of the blood is expelled by expiratory efforts, but some is aspirated into the lung, and at autopsy may be found widespread in the bronchi, in the form of branching clots or as coagulated masses within the alveoli.

Tuberculous Pneumonia.—Although the presence of tuberculosis may apparently predispose to various forms of bronchopneumonia, that form which is designated as tuberculous pneumonia is due primarily and principally to the tubercle bacillus. The organisms are numerous in the exudate and are probably transmitted through the air passages. Two forms are recognized although they are not necessarily connected and not always sharply distinguishable. *Gelatinous tuberculous pneumonia* is exudative in character. It rarely involves large areas of the lung, usually being present as a smaller involvement in the neighborhood of chronic ulcerative tuberculosis or tuberculous caseous pneumonia. Grossly, the involved portion is poorly defined and of irregular outline, covering areas two or three or more centimeters in diameter. The lung is not densely consolidated but of gelatinous consistency. The cut surface is smooth, non-granular, moist, semitranslucent and of pale gray or reddish-gray color. From it can be expressed a moderate amount of slightly cloudy colorless fluid. A few miliary and small conglomerate tubercles may be observed in the consolidated areas. Histologically, the alveoli show moderate capillary hyperemia, edema sometimes with fibrin, and considerable desquamation of lining cells. The cells are largely desquamated epithelial cells and endothelial cells (Pagel), lymphoid cells, a few polymorphonuclear leucocytes and an occasional red blood cell. Special staining usually shows a considerable number of tubercle bacilli. The smaller bronchi are involved in the same type of process.

Caseous tuberculous pneumonia may be the sequence of gelatinous tuberculous pneumonia or apparently may arise quite independently. There is no reason for supposing that gelatinous pneumonia necessarily progresses to caseous pneumonia. The latter process, however, is more distinctly destructive of lung tissue than exudative in character. Grossly, it may involve only a small part of the lung near chronic ulcerative or other form of tuberculosis. Not infrequently, however, it may be lobar in extent. Grossly, the affected part of the lung is definitely consolidated and of dense consistence. In the more extensive forms, the overlying pleura may show acute fibrinous pleurisy or a more definitely tuberculous form of pleurisy. The lung cuts readily and shows a slightly bulging, gray, or yellowish-gray, dry, non-granular cut surface

in which the alveolar markings are more or less obliterated. Tubercles are not usually found in this consolidated portion. The area is distinctly friable. It may resemble gray hepatization of lobar pneumonia but is distinguished because of the non-granularity of the cut surface, by the great friability and by the obliteration of various lung markings. The color is darker in deeply anthracotic lungs. Frequently, the caseous material breaks down and discharges into bronchi so as to leave single or multiple small cavities, lined by caseous material but only rarely showing a fibrous wall. Histologically, the mass is made up of caseous material showing shadows of exudate, of alveolar walls and of septa. Smaller bronchioles and smaller blood vessels are usually destroyed by the process. The larger bronchioles and bronchi show as a rule chronic catarrhal or tuberculous bronchitis. Blood vessels in the neighborhood of the consolidation may show fairly extensive protective thrombosis. The process may not be uniform in a given histological preparation, but shows in certain areas an exudative form of pneumonia similar to that seen histologically in gelatinous pneumonia, but usually much richer in cells. Tubercle bacilli are likely to be rich in the consolidated mass. The cavities appear histologically as places in which the caseous material has dropped out, and there is almost never any secondary infection and reaction as seen in the chronic ulcerative tuberculosis. Sections taken from the margins of the tuberculous pneumonia are likely to show miliary and conglomerate tubercles. When the latter is the case the process is easily identified. It can usually be distinguished from abscess or gangrene by the relatively slight inflammatory reaction in the non-involved parts of the lung. Such reaction when present consists, as is said above, of exudative processes similar to that seen in gelatinous pneumonia but may be present merely as a moderate infiltration of lymphoid cells and endothelial cells.

Syphilis.—This disease affects the lungs of the new born and infants much more commonly than it does the adult lung. In the former, it may appear either as single or multiple gummata or more especially as the so-called white pneumonia or pneumonia alba. The gummata have the usual gross and microscopical appearances and may be found in association with pneumonia alba. In the latter condition, large or small parts of the lung are consolidated and in the cut surface show either a glossy gray or a dull gray or even cheesy appearance. Histologically, the most characteristic feature is incomplete or entirely deficient development of the alveoli. In some cases, there are found only sprouts of bronchioles lined by cuboidal epithelium. In others, the alveoli are present as spaces smaller than normal. Around the bronchi and blood vessels in the septa and between the alveoli, there is a mass of connective tissue whose cellular constitution varies from short spindle cells resembling somewhat those of the mesoblast, and often with multiple processes, larger fibroblasts and adult connective tissue. The alveoli, except for their small size, may be normal or may contain desquamated epithelium which rapidly undergoes fatty degeneration, endothelial cells and lymphocytes. The connective tissue mass must be regarded as a direct evolution from mesoblastic tissue, which has not been

displaced by the growing alveoli because their development has been interrupted by the syphilitic process. Blood vessels often show distinct thickening of their walls, which may go on to complete obliteration. This, then, is rather a failure of development than a true pneumonia. On the other hand, cases are described as being syphilitic, in which the alveoli are well developed but contain desquamated epithelial cells showing fatty degeneration, endothelial and lymphoid cells, perhaps with a few leucocytes. Unless the spirochetes can be demonstrated, this latter form cannot be identified as syphilitic.

In the adult lung, gummata are occasionally observed and are usually found rather in the middle and upper parts of the lower lobe than in other situations. They are firmer than tubercles, show much less tendency to

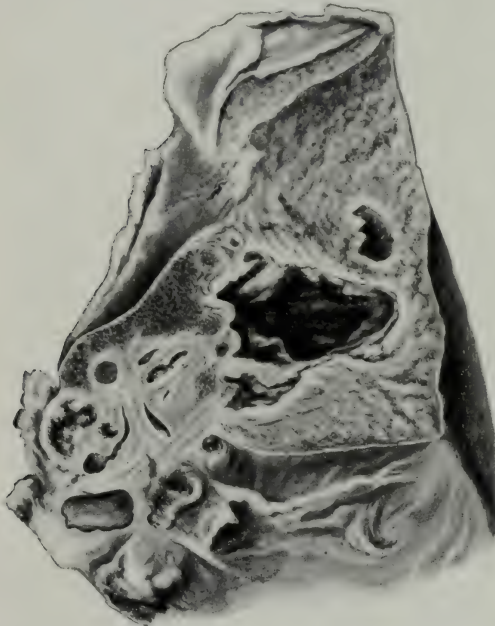


FIG. 257.—Syphilis of the lung showing gummata, extensive fibrosis and encapsulated cavity.

caseation, are more distinctly fibrosed and usually single. On the other hand, such a process may be accompanied by marked fibrosis, extending in more or less radial form from the gumma, sometimes along the blood vessels and bronchial tree and ultimately involving the pleura, which may show retraction because of the contraction of the connective tissue, the surface thus showing depressed folds, the so-called pulmo lobatus. When there are several foci of gumma formation associated with surrounding fibrosis, deformity of the lung may be very extensive. Pulmo lobatus, however, is extremely rare. Based largely upon roentgenographic findings, it is also said that the lung may show a more or less diffuse fibrosis as the result of

syphilitic involvement. In spite of the fact that such cases may improve under antisyphilitic treatment, it is impossible to state that it is of syphilitic nature until it has been confirmed by extensive pathological examination with the demonstration of spirochetes within the lesion. In our own experience such cases have usually been demonstrated at autopsy to be tuberculosis, tumor, or some other lesion not definitely syphilitic. Herxheimer's reviews give more extensive discussion of the topic, and it is also discussed by Powell and Hartley.

Other Granulomata.—When affecting the lung the bacillus of glanders may produce multiple small nodules somewhat resembling tubercles but much more likely to suppurate, single or multiple abscesses, or areas of bronchopneumonia which tend rapidly to break down and sometimes resemble caseous

pneumonia. There is usually a primary focus in the nose or elsewhere and the diagnosis depends very largely upon the recovery of the bacillus mallei.

Actinomycosis may affect the lung either as the result of aspiration from involvement of nose or mouth, or direct infection from esophagus or other neighboring organs, or extremely rarely by blood metastasis. The lesion in the lung does not differ materially from that elsewhere, except that in the margin of the actinomycotic nodule there is likely to be a certain amount of reactive pneumonia. As pointed out in the chapter on specific granulomata, infections by streptothrix and by blastomyces and other higher vegetable organisms may produce more or less diffuse consolidation and destruction of the lung, sometimes resembling tuberculosis, usually chronic in character and identified by finding the particular organism concerned.

Tumors of the Bronchi and Lungs.—Benign tumors are related particularly to the bronchi and include adenoma, usually originating from bronchial glands, papilloma from the bronchial mucosa, and, from the other structures, fibroma, lipoma, myoma, chondroma, and even osteoma. These usually occur as discrete tumors which rarely attain any considerable size but may produce serious effects by occlusion of parts of the bronchial tree.

Of the malignant tumors, sarcoma is much more rare than carcinoma. The sarcoma is usually single, occupying either the large part of the lobe or sometimes invading the entire lung. It is usually a massive infiltrating tumor which histologically appears as either a spindle cell sarcoma or a small round cell sarcoma, and occasionally shows polymorphous forms of cells. In addition, there may be combined sarcoma with more differentiated elements to constitute more especially chondrosarcoma and osteosarcoma. We have observed one chondrosarcoma which replaced an entire lung.

Primary carcinoma of the lung is not rare (Moses). Weller found forty cases of primary carcinoma of the bronchi or lungs in a total of 11,093 autopsies, an incidence of 0.36 per cent. It is usually stated that these tumors constitute from one to two per cent. of all tumors. In hospitals for chronic diseases the incidence is often distinctly higher. According to the figures of Adler, the greatest age incidence is in the sixth decade and there is general agreement that males are attacked more frequently than females. In order to establish a conclusive diagnosis, it is essential that a complete autopsy be performed so as to exclude all possibilities of other primary source, and that the diagnosis be confirmed microscopically. Three main gross forms are described, namely, a large nodular mass near the hilus of the lung, a diffuse infiltrative form and a miliary carcinosis. It is probable, however, as Moise suggests, that these may represent different stages of essentially the same process. In our own experience the hilic form has been most common. In this there is found near the hilus of the lung a poorly circumscribed, infiltrating mass of tumor tissue, showing variable degrees of necrosis, poorly vascularized, more or less necrotic and often associated with constriction of larger members of the bronchial tree. It appears to affect the middle and lower lobes more extensively than the upper lobes but may invade widely throughout the entire lung. Extensions

may be seen for a comparatively short distance along the bronchi and blood vessels. In the diffuse infiltrating form, the lesion at the hilus is not so striking and there are found, irregularly distributed throughout the lung, tumor masses poorly vascularized, pallid and necrotic, of irregular size and sometimes fusing to form very large masses. In miliary carcinosis there are innumerable nodules a few millimeters in diameter, translucent, white, and bulging in the cut surface, usually situated along the course of the lymphatic vessels. In this form it is particularly important to rule out the possibility of a primary focus in some other organ. Depending upon the involvement of the bronchi there may be more or less widespread areas of atelectasis. Foci of bronchopneumonia are not uncommonly a terminal accident. Usually the pleura is free from involvement, but in the more extensive cases there may be chronic adhesive pleurisy and occasionally definite involvement of the pleura by tumor metastases. The peribronchial and mediastinal lymph nodes are frequently involved. In the data of Adler, about 10 per cent. show no metastasis and 20 per cent. show metastasis limited to the thoracic cavity, in which involvement of the hilic lymph nodes is the most common. The remaining cases show more widespread metastasis which, according to Moise, involve in the approximate order of frequency, the regional lymph nodes, liver, kidney, lung, pericardium, abdominal lymph nodes, pleura, brain, adrenals, bone, cervical lymph nodes and heart. Histologically, the usual tumor is made up of cylindrical cell epithelium but, as Moise points out, there is often a lack of uniformity of cellular character in different parts of the same tumor. The cells are sometimes arranged to form acini, constituting an adenocarcinoma; cuboidal and polyhedral cells may be encountered, and in a few cases flat epithelium may also be found, representing probably a metaplasia of bronchial, epithelium, or tumor arising from squamous cells included in fetal or embryonal life. It is difficult to state positively that any of these tumors originate in the alveolar epithelium, and where identification of the point of origin has been possible, the bronchi are almost invariably implicated.

Secondary tumors of the lung may occur by direct extension as from the pleura or mediastinal lymph nodes. Much more commonly, however, secondary tumors arise as the result of blood transmission. Lymphatic transmission also occurs as is seen probably in the frequent involvement of the lung secondary to carcinoma of the breast. Tumor cells borne in the venous blood are especially likely to lodge in the pulmonary capillaries, their first point of obstruction in the circulation. Therefore, the metastasis of various forms of sarcoma is extremely common, as is also that from thyroid cancers, hypernephroma and chorionepithelioma. Secondary involvement from cancers may occur as the result of a generalized carcinomatosis in which metastasis is largely by the blood stream, and may also be secondary to cancer metastases in the liver which involve the blood vessels and are then transmitted to the lungs. Inasmuch as there is normally lymphoid tissue in the lungs, these organs may be involved in such systemic tumors as lymphosarcoma. The nodules vary in size from minute points to fairly large masses exceeding

several centimeters in diameter, fairly uniform in size, more or less compressing the surrounding lung tissue, rather rarely occluding important members of the bronchial tree, and showing the characters of the primary tumor. Occasionally, secondary extension of the tumor occurs through the lung, particularly by the lymphatics, and may thus be deposited in the mediastinal lymph nodes or by retrograde extension involve the subpleural lymphatics, sometimes producing the so-called "cancer en cuirasse."

Parasites.—In addition to such higher vegetable parasites as cause granulomatous lesions, aspergillus and certain forms of mucor are reported. Of the animal parasites monolocular or multilocular echinococcus cysts occur. In Japan and China an important infestation is that of distomum pulmonale or paragonimus Westermanni. Endameba coli may gain access by direct extension from liver abscess.

PLEURA

Hydrothorax.—Hydrothorax is essentially an edema of the pleural sac and may be caused by general conditions which lead to edema, such as heart failure and kidney disease, or local causes such as intrathoracic tumor or aneurysm, or inflammatory processes which may interfere with drainage of the blood or lymph. The fluid is clear, light yellow in color, limpid, of low specific gravity (about 1014), contains only a few endothelial cells and is not likely to clot upon standing. Ordinarily it collects in the lower and posterior parts of the pleural sac, but the distribution may be materially altered by preëxisting fibrous adhesions. These may be so widespread as to produce a sacculated form of hydrothorax, which may be supradiaphragmatic, under the thoracic wall, or interlobar, depending upon the position of the adhesions. In these cases the fibrous bands which constitute the adhesions may also show considerable edema. The fluid may be mixed with fat in fine or coarse emulsion, more especially when the hydrothorax is due to tumors or similar masses in the thorax, which not only compress veins but also compress the thoracic duct. The fatty material presumably gains access through leakage from the thoracic tributaries of the ducts. When compression is confined to the thoracic duct alone or when there is traumatic rupture of the duct, the material in the thorax may be practically pure chyle. A certain amount of fat may also be present when the hydrothorax occurs in lipemic individuals. When fat is contributed by fatty degeneration of cells in sufficient quantities to produce cloudiness or milkiess of the fluid, there is usually extensive tumor involvement of the pleura. The degree of cloudiness and the separation of fat upon standing depend essentially upon the type of emulsion. Excluding those cases in which the fat is due to fatty degeneration of cells or to lipemia, we apply to all others, in agreement with Blankenhorn, the name chylous hydrothorax, in which the fluid may vary considerably in degree of milkiess. We thus do away with the older terms pseudo-chylous and chyliform, used to represent lesser degrees of milkiess.

The lung shows degrees of atelectasis depending upon the amount of fluid.

It is small, firm, reduced in air content and the seat of passive hyperemia which gives it a dark red or a slate blue color. The negative pressure of the pleura remains normal and the atelectasis is due to decreased expansion because of filling of the sac. Only in those portions where the lung is actually immersed in the fluid and subject to its hydrostatic pressure is there a true compression atelectasis. When atelectasis is marked, the lung lies in the upper part of the chest more or less flattened against its hilus and the spinal column. Fibrous adhesions may alter the position. The physiological effects will be discussed after presenting the morbid anatomy of other conditions in which the contents of the pleura are increased.



FIG. 258.—Section of thoracic viscera including left parietal pleura in a case of acute empyema, showing position of fluid in left pleura and atelectasis of left lung. Small areas of bronchopneumonia are visible as dark areas in right lung. Army Medical Museum 16359.

Hemothorax.—This term is usually restricted to the presence of considerable quantities of free blood within the pleura. Such hemorrhage may be due to penetrating wounds of the thoracic wall, tearing of the lung by wounds, by needle punctures, or by fractured ribs, rupture of intrathoracic aneurysms and destructive processes such as tuberculosis and malignant tumors. Small hemorrhages into the substance of the visceral and parietal pleura are observed following death from asphyxia, certain poisons such as phosphorus, arsenic and mercuric chloride, severe infectious disease, the various hemorrhagic diseases, and following death from heart failure. As a rule, this is limited to petechiæ but occasionally considerable leakage may occur into the pleural cavity.

Inflammation of the Pleura.—Although strictly this should be referred to as pleuritis, nevertheless, common usage accepts the term pleurisy. Acute pleurisy may be fibrinous, fibrinoserous, purulent, putrid, and hemorrhagic.

Occasionally, bacteria gain access to the pleura from some unknown portal of entry. There are, however, many cases of fibrinoserous pleurisy in which bacteria are not ordinarily recoverable by the usual cultural methods, and no definite point of origin can be detected clinically. By injection into guinea pigs, however, many of these can be shown to be tuberculous in character. Acute pleurisy may develop in the course of pyemia and septicemia and various enteric infections, in which the organisms can usually be recovered from the pleural fluid. Presumably also blood borne are those pleurisies which occur in rheumatic fever and various acute infectious fevers of unknown cause. In many of these no organisms are recoverable. The most important cause of acute pleurisy, however, is direct extension from neighboring inflammation, the most striking example being the pleurisy which accompanies lobar pneumonia. Extension to the pleura may also occur from other types of pulmonary inflammation, from inflammation of the mediastinal lymph nodes, the pericardium, the peritoneum, especially where the latter inflammation is secondary to liver or spleen abscess or ulcer of the stomach. Extension may also occur from inflamed ribs and vertebræ and from infection entering through cancers or other destructive lesions of esophagus, stomach and bronchi.

Acute fibrinous pleurisy such as occurs in acute infectious diseases of various kinds, lobar pneumonia and tuberculous caseous pneumonia, shows upon the hyperemic visceral and parietal pleura, a layer of fibrin varying from a thin, yellow butter-like film in the less severe and earlier cases to a thick, rough, gray, shaggy mass in the more severe and long standing cases. In the latter the movements of the lungs are likely to whip the fibrin into fairly heavy bands. Histologically, there is the usual picture of fibrinous exudate enmeshing a few cells of exudative character. In the earlier stages there is swelling of the endothelium, followed by desquamation and disappearance. Organization begins early in the process. This becomes an acute fibrinoserous pleurisy when a considerable amount of serous exudate is poured out, thus constituting the pleurisy with effusion of the clinician. At autopsy, this diagnosis is not made unless the fluid in the pleural cavity exceeds 200 c.c. in amount. As withdrawn upon thoracentesis the fluid is usually light yellow in color, turbid, of relatively high specific gravity (about 1020–1023), rich in proteins of various kinds, and likely to coagulate upon standing. The fluid contains flakes of fibrin, desquamated endothelium, which may be more or less degenerate, and cells of the exudate, particularly polymorphonuclear leucocytes and lymphocytes.

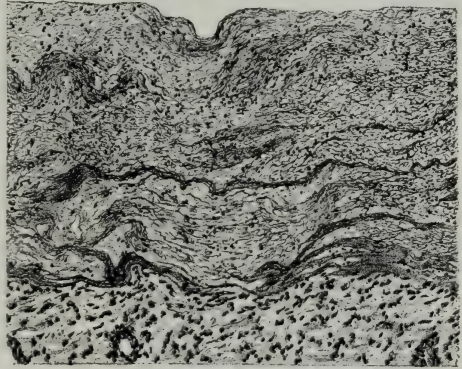


FIG. 259—Acute fibrinous pleurisy.

Acute purulent pleurisy, sometimes called pyothorax and usually called empyema, may represent an alteration of a fibrinous or fibrinoserous pleurisy or may originate as a purulent process. It may occur as the result of direct infection from wounds, as a part of pyemia and septicemia and may complicate various inflammations of the lungs, more particularly those due to streptococcus. In the earlier stages the pus is free in the pleural cavity, but there is apparently a rapid organization about the margin so that the pus tends to

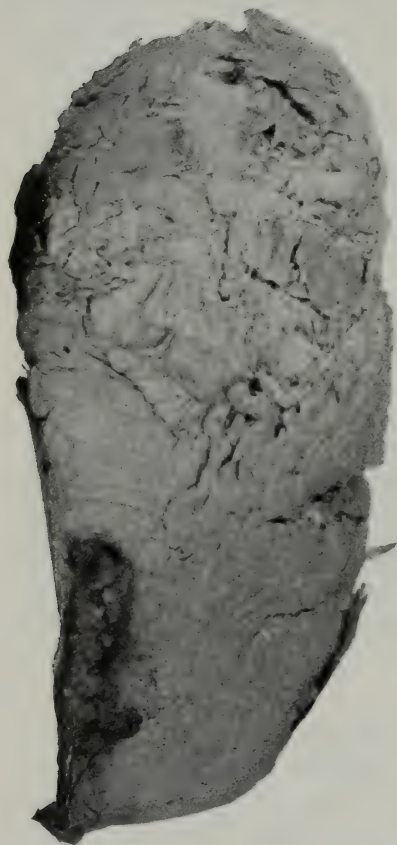


FIG. 260—Acute fibrinous pleurisy in late stage, more truly acute fibrinopurulent. Army Medical Museum 501.

become more or less localized in certain parts of the pleura. The pus is usually found under the thoracic wall in the lower part of the chest but may be observed overlying the diaphragm or between the lobes of the lung. The causative organisms are usually identified readily in the earlier stages of the process but as it becomes more chronic they are difficult to find.

Acute putrid or gangrenous pleurisy may be the result of gangrene of the lungs or the introduction of organisms ordinarily saprophytic through wounds of the thoracic wall. If gas forming organisms be present, there may be considerable accumulation of gas in the pleural cavity. As with empyema, provided the patient survives the acute stage of the process, encapsulation can progress fairly rapidly.

Acute hemorrhagic pleurisy may be seen where pleurisy occurs in connection with the various diseases mentioned as producing petechiæ of the pleura, but of outstanding importance are tuberculosis and malignant tumors of the pleura. In this condition, as in hemothorax, bile pigment may be found provided the blood remains a sufficient length of time in the pleural cavity.

Local Sequences of Acute Pleurisy.—It is probable that minor grades of acute fibrinous pleurisy may recover, with complete restitution to normal, or there may be simply a fibrous scar. If extensive, however, the granulation proceeding from both layers of the pleura results in the formation ultimately of fibrous adhesions between the two layers. This is to be regarded as a cicatrizing non-progressive condition which presumably has no functional significance, because respiration may go on normally in spite of complete obliteration of the pleural sac. It is usual to distinguish chronic fibrous pleurisy in which there is simple thickening of the layers of the pleura, chronic adhesive

pleurisy and chronic oblitative pleurisy. For the most part these represent scars, but more particularly in connection with chronic tuberculosis of the lung and with tumors of the pleura or the lung the condition may be progressive, and is then to be regarded as a true chronic inflammation. In hydrothorax the fluid can be removed readily by lymphatic absorption if the causative condition be cured. The same is true if an acute fibrinoseous pleurisy terminates early in its course. If very extensive and of long duration, the processes of organization going on in the pleura may so interfere with lymphatic drainage that natural removal is slow and sometimes incomplete. The purulent exudate of empyema may, after encapsulation has occurred, remain for extremely long periods of time, thus giving rise to prolonged absorption of the products of bacterial activity and protein decomposition. Occasionally, such conditions burrow through the thoracic wall, usually in the intercostal spaces but occasionally through the ribs, and drain spontaneously, but as a rule surgical intervention is necessary. If the exudate remain in situ for long periods, either with or without drainage, the secondary inflammatory processes of the pleura and in the compressed lung may by contraction lead to considerable deformity of the affected side of the chest.

Chronic Pleurisy.—As has been mentioned, many of the so-called forms of chronic pleurisy represent merely cicatrization. There are, however, chronic forms which are definitely progressive and these are most commonly observed in chronic tuberculosis of the lung. In addition to adhesions, the pleura may become enormously thickened attaining a thickness of 8 to 10 mm. or more. This is primarily a chronic progressive fibrosis which, however, usually shows an extensive hyalinization and frequently calcification. Rarely heteroplastic bone formation is observed.

Pneumothorax.—Air may gain access to the thoracic cavity either by wounds of the thoracic wall or by rupture of the lung into the pleural cavity, such as may occur in chronic ulcerative tuberculosis or other forms of tuberculosis of the lung, abscess, gangrene, tearing of the lung by fractured ribs or by exploratory needles, suppurative types of pneumonia, infected infarcts; and it is said to occur from rupture of an emphysematous lung or a normal lung with an extreme expiratory effort in coughing, etc. Gas forming bacteria may also lead to the presence of gas in the pleural cavity. External wounds which remain open may lead to the so-called open pneumothorax. Ruptures of diseased lungs may close down leaving a closed pneumothorax, or the tissues around the opening may operate in a valve-like fashion so that air enters during inspiration and cannot be expelled completely during expiration. Infection rapidly occurs and as usually seen the condition is a pyopneumothorax. The presence of organisms ordinarily saprophytic may transform this into a gangrenous pyopneumothorax. Clinically, the condition is distinguished, in addition to other features, by the fact that the fluid level is horizontal, because the collapse of the lung brings it above the level of the fluid and the latter remains in the bottom of the pleura. At autopsy, it is important to differentiate between air in the pleura as the result of postmortem

collapse of the lung and that which is there antemortem. For this purpose the skin of the chest may be dissected up so as to form a cup-like depression into which water is placed. A small cut through the intercostal muscle permits air to bubble through this fluid. Without disfiguring the skin a needle may be plunged through the thoracic wall, and if a lighted match or taper be held above it the escape of air or gas will extinguish it. Examination of the gas usually shows that it may be either normal air, or the oxygen may be reduced by absorption and the carbon dioxide increased over that of outside air. In putrid pneumothorax the carbon dioxide may be very rich, and more especially with the anaërobes, there may be enough hydrogen and methane produced to render the gas combustible.

Pneumothorax may be complicated by an interstitial emphysema of the lung, either following the rupture of diseased lungs or by the same trauma that caused the pneumothorax. Similarly, interstitial emphysema of the thoracic wall may occur, usually localized but sometimes extending up in the neck and down over the abdomen. Exploratory needle punctures may be followed by interstitial emphysema of the thoracic wall if air be in the pleura or be introduced during the puncture. This does not presuppose puncture of the lung since the air in the pleura may gain access to the subcutaneous structures during expiratory effort.

Tuberculosis of the Pleura.—Tubercle bacilli may produce in the pleura either tubercles or an exudative or productive type of inflammation. The former is referred to as tuberculosis of the pleura and the latter as tuberculous pleurisy. Tuberculosis of the pleura usually occurs as miliary tuberculosis and is either a part of a miliary tuberculosis of the lung or a generalized miliary tuberculosis. The tubercles appear as minute discrete gray or yellowish-gray nodules projecting slightly above the surface of the pleura but covered by endothelium. In cattle, the so-called “perlsucht” disease is not uncommon. This is a chronic productive type of tuberculosis, leading to the formation of sessile and sometimes pedunculated nodules several millimeters or a centimeter or more in diameter. They are usually firm, definitely fibrosed and on section show a variable amount of central caseation. Conditions approaching this are rarely found in man.

Tuberculous pleurisy may be acute fibrinous or more commonly an acute fibrinoserous pleurisy with a large quantity of fairly clear fluid which is sometimes tinged with blood. These forms are recognized anatomically, as a rule, by identification of extensive tuberculosis in the lung. The assurance that they are definitely tuberculous, however, must depend upon the presence of miliary tubercles in the pleura or the demonstration of tubercle bacilli in the exudate, which usually is done by animal inoculation. Sometimes in these conditions, there is extensive tubercle formation, not only of discrete miliary tubercles but of conglomerate tubercles. Chronic tuberculous pleurisy may be a chronic fibrous, a chronic adhesive, or chronic obliterative process. In many instances this is assumed to be tuberculous because of its intimate relation to chronic tuberculosis of the lung. On the other hand, the lesion may

show in the thickened pleura definite tubercle formation and sometimes extensive caseation. The great thickenings of the pleura in chronic pleurisy are usually tuberculous when not a part of chronic empyema, and the appearance of hyalinization and calcification is more common in the tuberculous form.

Other granulomatous lesions such as syphilis and actinomycosis are practically always secondary to the effects of these diseases in the lung, the mediastinal contents, or the thoracic wall.

Tumors of the Pleura.—Primary benign tumors are extremely uncommon and may include fibroma, lipoma, angioma, chondroma, and osteoma. Primary sarcomas are also unusual and may be spindle cell sarcoma, round cell sarcoma, or various forms of combined sarcoma, such as the fibrosarcoma and chondrosarcoma. Often included in this group is the so-called pleural endothelioma.

The pleural "endothelioma" or "mesothelioma" usually occurs in the lower part of the pleural sac as a more or less flat but nodular growth, involving both parietal and visceral pleura. In association there is practically always a considerable fibrosis of the pleura. The chronic pleurisy and the tumor growth may result in the formation of a more or less loculated mass, the locules containing thin serous or bloody fluid or inflammatory exudate. Similar fluids are found in the pleural sac. Histologically, the tumor is made up of large round cells, in variably sized foci with much central necrosis, or as is more frequently the case, numerous acini or pseudoacini are found. There is no definite evidence that these tumors arise from the mesothelial cells lining the pleural sac, or from the endothelium of the lymphatic vessels. Nodules, presumably secondary, are usually found in the mediastinal lymph nodes and more widespread metastasis is not uncommon. As a result of Robertson's studies, he concludes that many cases are carcinoma, either squamous or more often adenomatous, sarcoma, or unclassified, and in the last group he thinks that most of the instances are secondary cancers. Admitting that the condition may have a fairly definite clinical syndrome, there seems little reason for retaining the name endothelioma or mesothelioma and the tumors should be more accurately classified on an anatomical and histological basis.

Secondary tumors of the pleura are usually extensions from primary or, more commonly, secondary tumors of the lungs, but occasionally metastases occur extensively in the pleura with but little involvement of the lungs.

Physiological Alterations Due to Increased Pleural Contents.—Increases of fluid and solid contents may produce bulging of the chest without altering the normal negative pressure of the pleura. By reducing the normal curvature of the diaphragm, a moderate increase of pleural content leads to a restriction in the respiratory outward movement of the costal margin, whereas greater increases may lead to an inward instead of an outward movement (Hoover). Both experimentally and clinically large quantities of fluid may accumulate in the pleura without altering the negative pressure (Hewlett). Nevertheless, the weight of the column of fluid exerts pressure on that part of the lung which is immersed and contributes to the bulging of the intercostal spaces and chest. Injection of fluid into the dog's pleura produces a marked fall in systemic blood

pressure, due in part to compression and perhaps kinking of the intrathoracic vena cava, and in part to reduction of circulation through the lungs incident to diminution of respiratory aid to the pulmonary circulation and to actual compression of the lungs; perhaps in extreme cases there is compression of the pulmonary veins. Thus, there is deficient filling of the left and ultimately of the right atrium. Reduction of vital capacity varies with the degree of collapse of the lung.

The closed non-valvular pneumothorax operates in essentially the same way as do pleural fluids. Ventilation and gas interchange are not seriously interfered with. In fact, Hofbauer claims that in the resting individual no dyspnea occurs with only one-tenth the normal respiratory surface. In open pneumothorax there is atmospheric pressure in the affected side, so that the mediastinum moves toward the healthy side in inspiration and away from it in expiration, thus limiting the exchange of air. Dyspnea may be severe, the blood showing reduction of oxygen and increase of carbon dioxide. Rost suggests that this is due not only to the diminished lung excursion, but may also be contributed to by blowing air from the normal lung into the diseased side and sucking it back again in inspiration. Closure of the pneumothorax restores the oxygen and carbon dioxide content of the blood practically to normal. In valvular pneumothorax the inspiration of air into the pleura establishes atmospheric pressure which may be markedly increased during expiration, reading according to Hewlett a pressure of 3 to 10 mm. of mercury. The mediastinal contents are pushed toward the healthy side and the diaphragm depressed. Except for the compression of normal lung its respiratory action is not decreased, because with the pressure in the diseased side, the mediastinum moves toward the healthy side in expiration and away from it in inspiration. The pathological physiology of open pneumothorax is admirably discussed by Graham.

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CHAPTER XVI.

THE ALIMENTARY CANAL

MOUTH.
TONGUE.
TEETH.
SALIVARY GLANDS.
ESOPHAGUS.
STOMACH.
INTESTINES.
APPENDIX.
PERITONEUM.

MOUTH

Congenital Malformations.—The commonest malformation is harelip (cheiloschisis) which is often combined with cleft palate (anathoschisis). These are due to failure of union of the nasal process and the maxillary processes which go to form the lower part of the face. The middle third of the upper lip and the premaxillary part of the upper jaw are contributed by the nasal process. Since harelip is due to failure of fusion of nasal and maxillary processes, it occurs at the outer margin of the middle third of the upper lip and may be single or double. There may be only a slight indentation of the lip, or the fissure may extend upward and communicate with the anterior nares. Median harelip is extremely rare. In the more extensive cases of unilateral or bilateral harelip there is an associated cleft palate, the fissures in the latter extending to either side of the intermaxillary bone, which provides the incisor teeth, and often accompanied by altered or incomplete development of these teeth. When it occurs in the posterior part of the hard palate, the fissure is median because the palatal plates are provided by the maxillary processes. Fissures of the lower lip are rare. The development of the lips may proceed too far toward the median line, leaving only a small opening (microstomia), or there may be a failure of development laterally, leaving a wide mouth fissure sometimes extending nearly to the ears (macrostomia). Numerous other more severe faults of development which occur are usually incompatible with life. These are treated in the texts on embryology and congenital malformations.

Macrocheilia has been referred to in the chapter on tumors as a congenital tumor-like enlargement of the lymphatic vessels, which may be progressive.

Pigmentations.—The most important pigmentation is that which often occurs upon the lateral and inferior aspect of the tongue and in the buccal mucosa in Addison's disease. This has diagnostic significance, especially in negroes.

Acute catarrhal stomatitis is more common in children than in adults. It may be due to mechanical, thermal or chemical irritants, may be the result of extension from inflammations of the pharynx and nose, may accompany acute infectious diseases such as scarlet fever, measles, typhoid fever, smallpox, etc., is common during the teething period and often accompanies gastric distur-

bances, particularly acute catarrhal gastritis. The mucous membrane is red, swollen, somewhat edematous and may show either excess or reduction of mucous secretion. Small white spots may appear due to necrosis or desquamation of the surface epithelium. Histologically, there is, in addition to surface degeneration, hyperemia and edema, and a moderate infiltration of lymphoid cells and leucocytes.

Acute vesicular stomatitis may be caused by various irritants such as heat, or carious teeth, or may be an extension from vesicular or pustular processes about the lip, more particularly herpes, eczema and smallpox. The ordinary form is usually localized about the tip of the tongue, the lips and the buccal mucous membrane, where the vesicles are formed by a serous exudate under the squamous epithelium. There is usually a neighboring catarrhal inflammation and, if the vesicles rupture, small

ulcers are formed. Early in the course of smallpox the hard, shot-like nodules may be found in the mucosa covering the hard and soft palate.

Acute fibrinous stomatitis may be either an extension to the mucous membrane of the soft palate and lateral faucial walls, or to the base of the tongue, from diphtheria and other inflammations of the tonsils, or may be produced by the action of corrosive chemicals. Also fibrinous in character is the so-called *aphthous stomatitis* which is more common in children during the period of teething but may accompany various acute infectious diseases. In adults it is more



FIG. 261—Complete unilateral harelip and cleft palate, showing marked flattening of ala nasi and deviation of nasal septum. Patient five months of age. Courtesy of W. B. Davis, International Clinics.

common in women during periods of pregnancy, the puerperium or during menstruation. The inflammation of the membranes is accompanied by the formation of slightly elevated yellowish-white plaques of irregular shape and size which, histologically, show an exudate beneath the epithelium containing variable amounts of fibrin. Desquamation of the superficial epithelium may produce ulcers.

Acute ulcerative stomatitis may occur in young, ill-nourished children and is commonly associated with the presence of fusiform bacilli and spirochetes of Vincent. It also occurs in scurvy and in poisoning by mercury, lead, copper, and phosphorus. The lesions usually begin about the margins of the teeth, with hyperemia and swelling, and in scurvy there is a certain amount of hemorrhage. Ulceration rapidly proceeds along the gums and may involve the floor of the mouth and the teeth. Necrosis of the jaw bone may occur, particularly in cases of phosphorus poisoning. Infection may extend into the dental processes and is often followed by dropping out of teeth.

Acute gangrenous stomatitis may be the result of invasion of wounds by saprophytic organisms, may follow upon acute ulcerative stomatitis, or may occur as noma. The para-infectious disease called *noma* is a gangrenous process in the cheeks which may be primary there or may follow acute gangrenous stomatitis elsewhere. It is more common in young children, and is likely to be associated with scarlatina, measles, typhoid fever or other acute infectious diseases. The process rapidly extends through all the tissues of the cheek, appearing ultimately upon the cutaneous surface. It cannot be said that any special type of organism produces this condition but, as in other gangrenous inflammations of the mouth, the fusiform bacilli and spirochetes of Vincent are commonly found. The disease is usually fatal.

Thrush is a form of stomatitis due to *oidium albicans*, occurring in ill-nourished children or in children and adults suffering from prolonged exhausting diseases. Slightly elevated, white or yellowish-white patches of irregular shape and size occur in various parts of the mouth, due to the growth in or upon the epithelium of the particular yeast concerned. This condition may extend to the pharynx, esophagus and even to the upper respiratory tract.

Koplik's spots are bluish-white, slightly elevated spots, a few millimeters in diameter, fairly numerous, which occur in the posterior parts of the cheeks in the preëruptive stage of measles and constitute an important diagnostic sign. Similar spots may appear even earlier in the lachrymal caruncle. Histologically, there is found keratinization of the superficial epithelium under which is a collection of polymorphonuclear leucocytes.

Tropical sprue shows acute or chronic catarrh of the mouth often with aphthous spots. The catarrh may be present in the entire alimentary canal. The disease is probably due to monilia psilosis of Ashford, the activity of which may be enhanced by dietary deficiency (see Bastedo and Famulener). In *pellagra* the tongue shows severe inflammation and the intestinal canal may be the seat of acute catarrh or a chronic atrophic catarrh (Roberts).

Ludwig's angina is a severe acute inflammation of the floor of the mouth usually originating in inflammations of the submaxillary glands or in the lymph nodes. Suppuration is common, the process by its extent constituting a phlegmon, and sometimes gangrene supervenes. It may extend to the neck and even to the mediastinum. It is often fatal either because of the infection or because of edema of the glottis.

Chronic stomatitis is characterized by a more or less diffuse thickening and keratinization of the superficial epithelium, with fibrosis of the underlying connective tissue and enlargement of the lymphoid nodules. The process when involving the filiform papillæ of the tongue may give it an extremely shaggy appearance. *Leucoplakia oris*, or buccalis, is more localized. Fox points out that it affects especially middle-aged men and is rare in women and in negroes. The direct cause seems to be local irritation particularly by tobacco, and syphilis is a predisposing cause in a large number of cases. The patches are of irregular shape and sometimes are referred to as geographic. They may appear

upon lips, buccal mucous membranes, tongue, or other parts of the mouth, as slightly elevated, hard, clearly defined, yellowish or grayish-white plaques. Histologically, the entire epithelial covering is thickened, and there is extensive keratinization of the epithelium between the papillæ of the supporting connective tissue, and the latter frequently shows a low grade subacute or chronic inflammation. It may lead to cancer but may exist for years without malignant change.

Infectious Granulomata.—Of these syphilis is the most frequent. Chancre may appear on lips, the buccal mucosa, particularly near the angles of the mouth, upon the tip of the tongue and even upon the tonsils. The secondary lesions may include an erythematous eruption or, more commonly, the so-called mucous patches. These are at first reddened areas, rapidly becoming slightly elevated plaques a few millimeters or a centimeter or more in diameter, fairly well defined, soft, and bluish-gray in color. Desquamation of the epithelium may leave shallow ulcers with a moist, smooth, only slightly reddened base. Gummata appear in the deeper tissues rather than upon the surface and finally produce projecting masses. In our own experience these have been more common in the soft palate than in other situations. They may ulcerate and lead to severe hemorrhage.

Tuberculosis may occur as an extension from tuberculous lupus of the face, or as miliary or small conglomerate tubercles which are superficial and tend to ulcerate. Tubercles may appear in any part of the mouth but are most common on the tongue, gums, hard and soft palate (Ivy and Appleton). This type of lesion is practically always secondary to pulmonary tuberculosis, sometimes localizing in the mouth as the result of abrasions such as are produced by carious teeth, and indeed this may first call attention to the pulmonary disease.

Leprosy may appear in the mouth, particularly in the tubercular form. Actinomycosis and glanders also occur in the mouth.

Tumors.—Fibroma and lipoma may occur in any part of the mouth, more commonly as somewhat pedunculated tumors of the mucous surface of the lips. Papillomata may occur in any part of the mouth, as is true also of the hemangioma. The lymphangioma has been referred to above. Dermoid cysts and other varieties of teratoma may occur, apparently as the result of faults in development of the branchial clefts.

With the exception of tumors of the tongue, which will be referred to subsequently, cancer of the mouth, although it may develop anywhere, is most frequent upon the lower lip. Chronic irritation is a frequent precursor. Cancer of the buccal surface may follow the prolonged irritation of jagged teeth, or the persistent chewing of betel nut. Cancer of the lip may follow the repeated irritation of a rough pipe stem. In the latter situation it appears as a small nodular or ulcerative process, chronic in character. Histologically, it usually shows the picture of squamous epithelioma. Metastases occur to the sublingual or submaxillary glands. Sarcoma is extremely rare.

TONGUE

Congenital Malformations.—The anterior portion or the entire tongue may be congenitally absent. The tip may be bifurcated or there may be actual lobulation of the tongue. Developmental fusion with the floor of the mouth or with the gums or even with the roof of the mouth are observed. Of most practical importance, however, is that condition known as “tongue-tie” in which the frenum is abnormally short, or extends out as far as the tip of the tongue. Remnants of the thyroglossal duct may produce cysts at the base of the tongue. These are usually lined by ciliated epithelium, and occasionally colloid may be produced in small acinar spaces.

Retrogressive Processes.—Amyloid is occasionally observed in the tongue. Edema may be seen, particularly in connection with myxedema. Paralysis, such as may be due to lesion of the hypoglossal nerve in bulbar palsy, may lead to atrophy of the tongue.

Inflammations.—Any of the inflammations discussed above as affecting the mouth may also affect the mucosa of the tongue. The coated tongue of fever is usually due to a low grade acute catarrhal glossitis, the coating being made up principally of desquamated epithelium, mucus and large numbers of bacteria, usually the normal inhabitants of the mouth. Abscess and other forms of interstitial inflammation as well as gangrene may occur from wounds of the tongue. A rare inflammation of subacute or chronic character is that known as *geographic tongue*. This occurs in infants and young children but rarely in adults. It sometimes shows a familial distribution. It usually begins near the tip of the tongue as a somewhat edematous yellowish-white spot, which spreads in all directions and very soon shows desquamation of the central part, leaving a smooth red surface lined by deeper epithelium. As it continues to spread, there occurs central healing, the process usually running its course in about two weeks. Secondary areas may fuse with others, the whole process having an irregular outline suggesting a map-like contour. Recurrences are frequent and the disease may last over several years.

Infectious Granulomata.—Tuberculosis usually occurs in association with pulmonary tuberculosis. Most commonly it appears as a conglomerate ulcerative process, not infrequently along the edge of the tongue, where ulceration may have been produced by a carious tooth (see Morrow and Miller). Syphilis may be present as chancre, secondary mucous patches or in the form

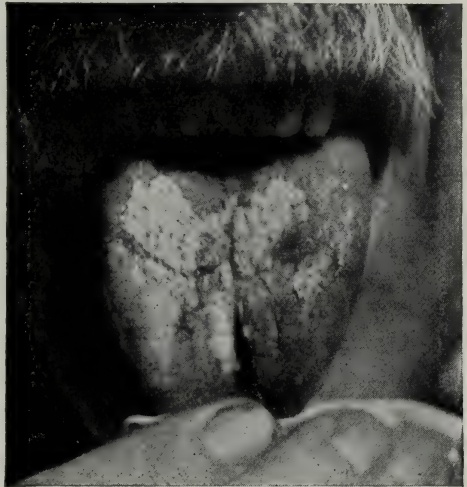


FIG. 262—Leucoplakia of the tongue. From Hartzell, *Diseases of the Skin*.

of gumma, the last being deep seated in the organ but occasionally appearing near the surface and ulcerating. Atrophy of the papillæ of the base of the tongue is said to occur in late acquired syphilis.

Tumors.—Fibroma and lipoma may occur rarely as masses in the substance of the tongue or may appear as pedunculated tumors. Hemangioma is also rare. Lymphangioma is usually congenital and constitutes the condition known as macroglossia. As the result of fetal inclusion, thyroid and parathy-

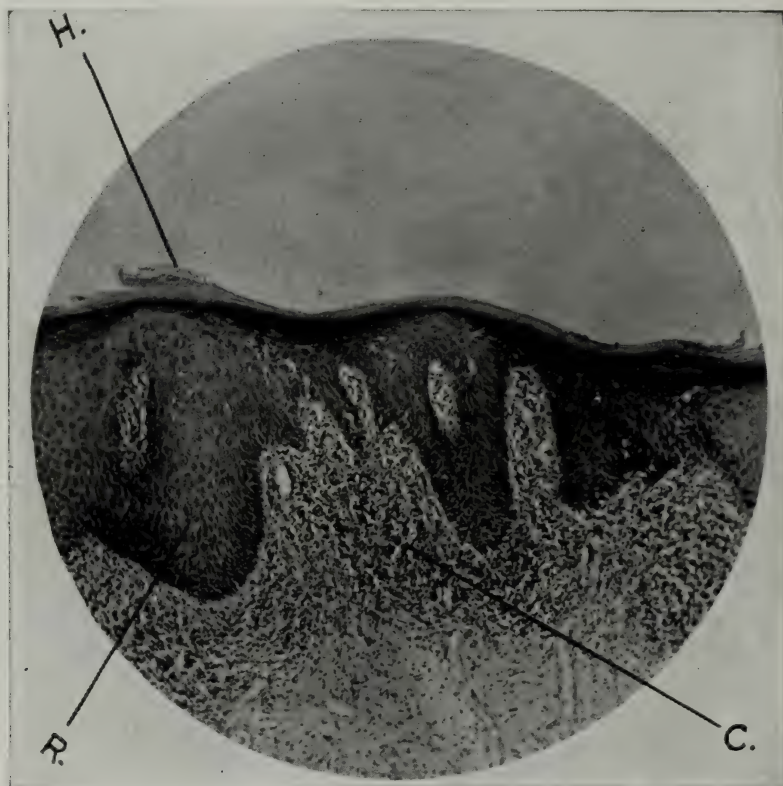


FIG. 263—Section through a small patch of leucoplakia of the tongue. H, thick horny layer of the mucous membrane; R, rete markedly increased in breadth; C, cellular exudate in upper part of the corium composed of polymorphonuclear leucocytes, plasma cells and a considerable number of small "Mastzellen." From Hartzell, Diseases of the Skin.

roid tumors have been observed (Wood). In addition to cysts formed from thyroglossal ducts, cysts due to occlusion of salivary ducts are also observed in the under surface of the tongue, the condition being known as *ranula*.

Carcinoma of the tongue is practically always squamous epithelioma and frequently there is a history of chronic irritation either from smoking or from carious teeth. It is ordinarily of slow growth and may show metastasis to the sublingual and submaxillary lymph nodes. Sarcoma is extremely rare but may occur as a diffuse interstitial growth or sometimes as a projecting nodular growth. Even more uncommon is the occurrence of rhabdomyoma.

TEETH

Dental Caries.—This begins in the enamel, usually in the sulci of the crown or near the lower margin of the enamel, as an opacity which may become yellow or dark brown. Disintegration and decalcification of the enamel are followed by sloughing and the process then involves the dentine. According to Marshall the lesion may be predisposed to by anatomical fault in the structure of the tooth, by the influence of dietary deficiencies, by deficiencies of internal secretion, especially of parathyroids, but more directly of importance are alterations of saliva and action of bacteria. The saliva is a buffer of complex composition (see Dodds), and it is unlikely that its acidity is of importance except as it is acted upon by bacteria. The organism especially concerned is the *bacillus acidophilus odontolyticus* which may occur in two strains. Although Clark considers that the action of *streptococcus mutans* is necessary to break down the enamel before *bacillus acidophilus* can operate, McIntosh, James and Lazarus-Barlow find that the latter organism can produce sufficient acid to affect the enamel directly, and this view is supported by Bunting and Palmerlee. When the pulp is invaded, it becomes inflamed, exhibiting hyperemia, swelling and pain, followed by necrosis or suppuration or both. This invasion may occur by extension of the caries or by growth of the organisms through the dentinal canals. As it extends down the pulp canal, the periodontal membrane may become inflamed, to produce a periodontitis which may suppurate and form the true root-abscess. Infection of the bone is not common. If the tooth remain, the periodontitis may become chronic and sharply localized with the production of the so-called periodontal granuloma, in which there is fibrosis, infiltration of lymphoid and endothelial cells and varying degrees of calcification. If infection of the jaw occur, the resulting osteomyelitic abscess may rupture through the gum or, more particularly in the lower jaw, may point through the skin surface.

Pyorrhea alveolaris, periodontoclasia, or Rigg's disease, is a chronic suppurative inflammation of the periodontal membrane near the gum margins of a group of several teeth, which occurs most often in middle life. There is almost constantly an associated dental caries. Constitutional factors, calcification in the periodontal space, salivary reactions, various bacteria, treponemata and endamebæ have been discussed in various publications without indicating finally the cause or causes which operate (Hall). Downward extension may cause extensive caries of the roots or a necrosis of the pulp from occluded blood supply. The teeth are often loose due to destruction of the periodontal membrane and may drop out. Various organisms are associated such as *streptococcus viridans*, fusiform bacilli and spirochetes, and mouth amebæ. The presence of periodontoclasia may favor phosphorus necrosis, mercurial stomatitis and the blue line of plumbism.

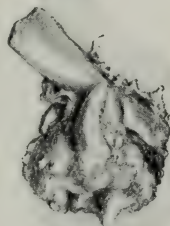


FIG. 264—Gross drawing of odontoma.

Sequences of Dental Infections.—In children dental caries is often the cause of acute hyperplastic lymphadenitis of the floor of the mouth and of the neck. Caries and pyorrhea may be the portal of entry of actinomycosis. Aspiration of fusiform bacilli and spirochetes may lead to pulmonary gangrene. The extraction of carious teeth, especially when there is an extensive periodontitis or osteomyelitis, may occasionally be followed by septicemia, or by wide local spreading of inflammation and necrosis. Indeed septicemia may occur without extraction. It is possible that the organisms of articular rheumatism, endocarditis and other infectious diseases may enter the body through the

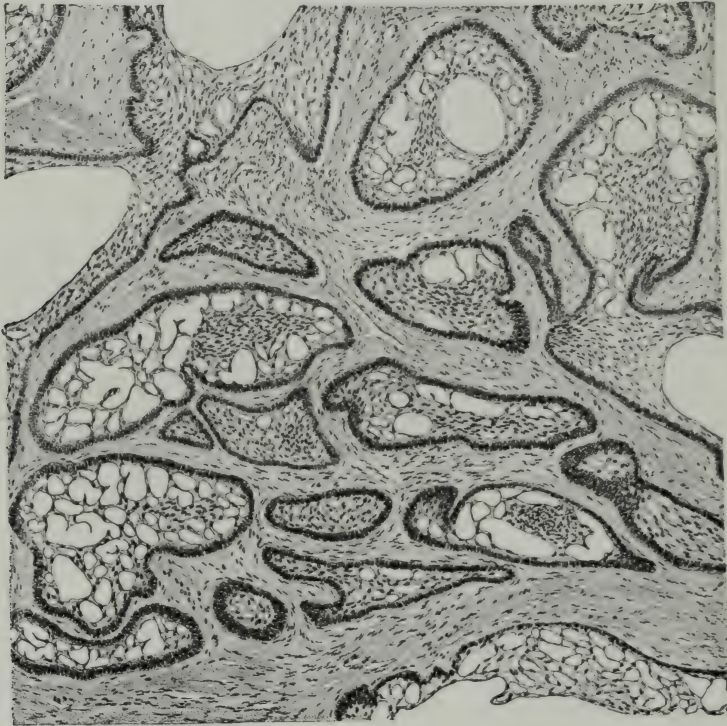


FIG. 265—Cystic adamantinoma.

medium of dental and periodontal foci of infection. We believe, however, that this possibility has been much over-emphasized in recent medical literature.

Tumors.—Various connective tissue and epithelial tumors, originate in the tissues of the jaw. The teeth may show failure of eruption, various malformations and the presence of small tumors originating in dentine, cementum or enamel. There are in addition solid and cystic tumors or tumor-like growths usually derived from the dental anlage or partially developed tooth. The odontoma is made up of constituents of the adult tooth in varying proportions. The solid soft forms are usually small and contain principally derivatives of pulp tissue and periodontal membrane. The hard forms may appear as simple enlargements of the root made up principally of dentine, or as

larger masses looking like a coiled or convoluted root, containing dentine, enamel and osseous tissue. As mentioned in the chapter on tumors, the adamantinoma, an epithelial tumor arising from the enamel organ appears frequently in solid form. New classifies the cystic odontomata as type A, the so-called dental or root cysts, and type B the so-called follicular cysts, which often contain a partially formed tooth. He, however, prefers not to use the term follicular, since no definite proof exists that the condition originates in the follicles. The term dentigerous cyst, which may apply to either form is no longer generally accepted. The simple cysts of type A are rarely large, occur more commonly in the upper jaw, have a thin bony wall, are lined by more or less flattened epithelium which may disappear, and are probably derived from remnants of the dental ridge. Type B occurs with equal frequency in upper and lower jaws; a tooth is usually missing from the set and the crown and parts of the root of a tooth are usually found in the cyst; there is a thin bony wall and an epithelial lining. Although this is not proven, Bland-Sutton believes that these originate in a tooth follicle. Somewhat similar periodontal or extracapsular cysts, usually small, may be found near the teeth but not definitely attached, with a soft wall lined by cylindrical or stratified squamous epithelium and probably derived from epithelial remnants in the jaw. The cystic adamantinoma is usually multilocular in character.

SALIVARY GLANDS

Inflammations.—These may occur in any of the salivary glands as the result of extension from the mouth or infection of the ducts, particularly when calculi are present, or, more especially in the parotid, may complicate septicaemia or pyemia. Of great importance is acute epidemic or infectious parotitis, or *mumps*, a highly contagious disease. This shows tender swelling of the parotid region, usually bilateral, with mild fever, but without leucocytosis. Various bacteria have been considered the cause but Wollstein's experiments point toward a filterable virus. The disease lasts from one to two weeks. It may also involve the submaxillary glands (Rotch). It is a catarrhal inflammation of the ducts and gland with hyperemia, edema, cloudy swelling and desquamation of epithelium and a mild infiltration of lymphocytes and a few leucocytes into the interstitial tissues. It usually subsides with complete restoration to normal. The most common complication is similar inflammation of the testis and sometimes of the epididymis, usually unilateral and occurring most commonly in boys at puberty. Recovery may be complete or there may be slight fibrosis and atrophy. Acute oöphoritis, acute mastitis, and even acute pancreatitis may occur.

Chronic inflammations may occur as the result of acute inflammations, calculi and plumbism or there may be no determinable cause. There is usually much fibrosis which, even with atrophy of the parenchyma, may lead to considerable enlargement and induration.

Salivary Calculi are usually phosphatic but may be made of carbonates. Bacterial and mucous masses may constitute obstructive concretions. Cal-

culi may attain great size and are more common in the submaxillary and sublingual ducts than in the ducts of Stensen. Obstruction by inflammation, by surrounding fibrosis or by calculi, leads to distension of the ducts and glands, sialoceles, with subsequent atrophy of the glands. Obstruction of the sublingual duct may cause distension near the orifice under the tongue, producing ranula.

Infectious Granulomata.—Tuberculosis may occur as the miliary or conglomerate form and the latter may constitute the so-called "cold abscess." Syphilis may produce gumma. Actinomycosis may also occur.

Tumors.—Adenoma, fibroma, carcinoma and sarcoma may occur in any of the salivary glands. Perhaps the commonest is the mixed tumor of the parotid, described in the chapter on tumors as made up of cellular, probably epithelial, myxomatous, chondromatous and cylindromatous elements. This may recur after removal and may become definitely malignant, especially after several recurrences.

THROAT

Congenital Malformations.—Defects in the final development and closure of the branchial clefts may result in the formation of cysts in the neighborhood of the fauces and pharynx. Either as the result of inflammation or of congenital malformation there may be stenosis or atresia of the fauces, of the soft palate and pharynx. Esophagopharyngeal diverticula are discussed under esophagus.

Inflammations.—Acute catarrhal inflammations of the pharynx, tonsils, nasopharynx, and fauces are common in connection with colds, and various organisms may be isolated, including streptococcus, staphylococcus, pneumococcus, micrococcus catarrhalis, etc. These organisms, more particularly the streptococcus, may be the cause of epidemic sore throat. Similarly, catarrhal inflammation of varying severity may affect these parts in a variety of acute infectious diseases, notably scarlatina and diphtheria. The tonsils are likely to be the seat of an acute hyperplasia, not only in connection with the diseases mentioned above and accompanying catarrhal inflammations, but also in diseases where there is general lymphadenoid involvement, as for example, typhoid fever.

In acute follicular tonsillitis there is likely to be acute catarrhal inflammation of the fauces and pharynx. The tonsils are the seat of acute hyperplasia and the crypts are likely to be filled with leucocytic, fibrinous, necrotic or even suppurative material which appears upon the tonsillar surface as many foci of exudate 1 or 2 mm. in diameter. Streptococcus hemolyticus, as well as other organisms, may produce this condition.

Diphtheria, the general manifestations of which have been discussed in the chapter on infectious diseases, is likely to originate upon one or both tonsils. There is an associated catarrhal inflammation of fauces and pharynx as well as an acute hyperplasia on the tonsil itself. The surface shows the smooth white, or pale yellow, well defined, easily detached fibrinous exudate, which subsequently becomes yellow and rough on the outer surface, and more firmly attached. The diphtheritic inflammation may extend so as to involve fauces, nasopharynx, and larynx.

Vincent's angina, due to the spirochetes of Vincent and the associated fusiform bacilli, is commonly primary upon the tonsils but may appear anywhere else in the neighborhood. There is at first a superficial destruction of the tissues which later produces a ragged, fairly well defined ulcer with gray, shaggy, necrotic base. The ulceration may extend widely both laterally and deeply.

Acute suppurative inflammation may involve any part of the throat, more especially as the result of invasion by streptococci or staphylococci. Beginning in the tonsils it may extend fairly widely in the peritonsillar tissues, constituting the condition commonly called quinsy or, more properly, acute suppurative peritonsillitis. Suppurative inflammations of the throat may also extend into the retropharyngeal tissues producing retropharyngeal abscess, which may cause serious obstruction to breathing. Tuberculosis may produce retropharyngeal "cold abscess."

Agranulocytic Angina.—This is apparently a clinical entity, in which there are destructive ulcerative lesions of the throat, leucopenia, great reduction or absence of granular cells in the blood and bone marrow, and often icterus (Lovett). It affects principally middle aged women and is fatal. Although suspicion is directed toward bacillus pyocyaneus, no cause can be regarded as established.

Chronic Inflammations.—Chronic pharyngitis is not uncommon in speakers and singers, particularly those with improper voice production. It is more especially a disease of adults and may appear as a granular form with hyperplasia of the small lymphadenoid foci in the pharynx. Chronic tonsillitis may appear at any time of life but is more common in childhood when it apparently is the result of repeated attacks of acute tonsillitis, or may be primarily chronic. It is essentially a subacute or chronic hyperplasia of the lymphadenoid tissues, often showing enlargement of the germinal centers, increase in number of small lymphocytes and sometimes definite fibrosis. In association the crypts are often filled with desquamated cells and necrotic debris. This material is a favorable culture medium for various forms of bacteria and can be a source of absorption of bacterial products. Sometimes the bacteria and necrotic material are arranged in radial form, simulating the granules of actinomycosis (Davis). The necrotic material may become calcified. This hyperplasia is the so-called hypertrophy of the tonsils and may affect not only the faucial tonsils, but also the pharyngeal tonsils, constituting the so-called adenoids. Leucoplakia, similar to that seen in other parts of the mouth, occasionally occurs upon the tonsils and pharynx.

The special types of lymphoid hyperplasia such as occur in leucemia, Hodgkin's disease, and similar conditions, may also produce enlargement of the tonsils.

Infectious Granulomata.—Tuberculosis may be seen in these regions similar to that affecting other parts of the mouth. Tuberculous retropharyngeal abscess occasionally occurs. Of considerable importance is tuberculosis of the tonsil which occurs in from 2 to 3 per cent. of all tonsils removed for

pathological examination. Weller divides tonsillar tuberculosis into three types, the focal crypt infection, the ulcerative lupus-like lesion, and diffuse miliary tuberculosis. How much significance tuberculosis of the tonsil has as a portal of entry of the organism into the body is unknown. It is often associated with other tuberculous lesions of the body and is especially frequent in connection with tuberculosis of the cervical lymph nodes; whether as a primary portal of entry or as secondary to the lymph node involvement, is not definitely known.

Mucous patches of secondary syphilis are not uncommon in the throat. Gumma may form in the tonsils, fauces and pharynx and may ulcerate and occasionally produce severe hemorrhage. More rarely chancre occurs upon the tonsils. Rhinoscleroma not uncommonly extends so as to involve the tissues of the throat. According to Davis, actinomycosis does not occur in the human tonsil, and in suspected cases careful distinction must be made between this and actinomyces-like bodies found in chronic hyperplastic tonsillitis.

General Infection from Tonsils.—Much discussion has arisen as to whether or not remote metastatic infections may be spread from the tonsils, especially such conditions as rheumatic arthritis, endocarditis, etc. Clinical evidence of importance has been adduced, but final experimental support has not been brought forward. Crowe points out that this is unlikely from the surface, but that the rich vascularization of the connective tissue papillæ in the crypts affords a possible portal of entry from diseased crypts.

Tumors.—Epignathus, a tumor-like embryonal mixture of tissues, appears in the pharyngeal wall. Fibroma, lipoma, chondroma, osteochondroma, angioma, and other benign tumors are occasionally found in the tissues of the throat. Papilloma covered by stratified squamous epithelium may appear in any part of the throat, but it is said to be most common about the uvula.

Primary carcinoma, usually a squamous epithelioma, may originate in the tonsils, soft palate or pharynx. Metastasis is usually local because death from hemorrhage, suffocation, or pneumonia, usually occurs before widespread metastasis. Lymphosarcoma is sometimes primary in the tonsil, almost always with associated involvement of the cervical lymph nodes. The tonsils may be involved secondarily when lymphosarcoma is primary elsewhere. Other sarcomas of the throat are unusual and distinguishable from the lymphosarcoma with difficulty. These are usually round cell sarcomas which are likely to begin in the neighborhood of the soft palate. Secondary involvement of the throat by cancer is uncommon, but is more likely to be the result of metastasis from tongue or larynx cancers than from malignant tumors in other situations.

ESOPHAGUS

Congenital Malformations.—The commonest of these is an association of atresia with communication between esophagus and trachea, esophago-tracheal fistula. The esophagus itself may be simply narrowed or completely interrupted; in the latter case the upper part is blind and the lower part communicates with the trachea (Weiss, Vinson). There may be congenital stenosis without tracheal fistula and there may be a congenital dilatation. Very rarely

congenital aplasia, or agenesis of the esophagus, occurs in which both upper and lower parts terminate blindly, connected by a fibrosed muscular cord. This condition is usually associated with more general congenital malformations.

Retrogressive Processes.—Postmortem softening is common at the lower end of the esophagus, due to the digestive action of gastric juice. Active hyperemia occurs in the early stage of inflammation. Edema of the lower end of the esophagus is said to occur after severe vomiting and sometimes accompanies acute general peritonitis. Passive hyperemia is common in chronic heart and lung diseases, and is of importance because it may lead to the production of small submucous hemorrhages which break down to produce hemorrhagic erosions. Varicose dilatation of the veins of the upper end of the esophagus sometimes occurs, in old people and also in others who, because of intrathoracic

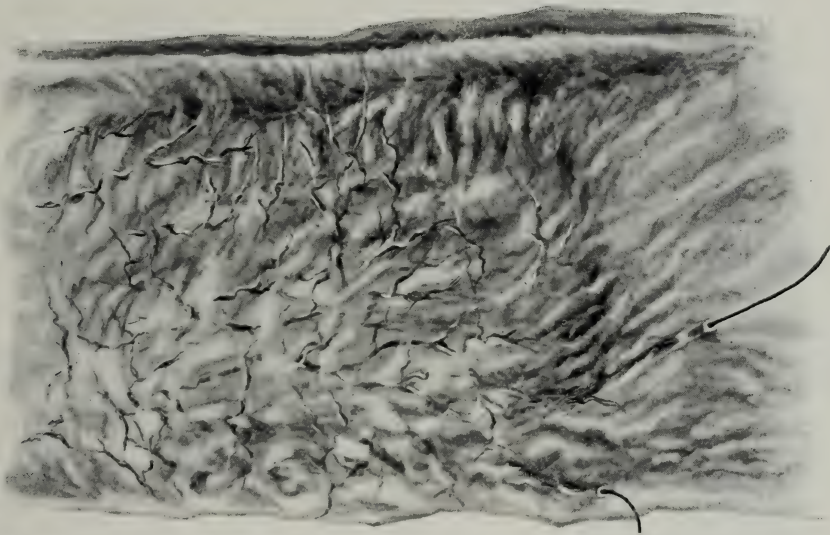


FIG. 266—Varices of lower end of esophagus in a case of atrophic cirrhosis of liver. Horse hairs have been inserted at two points of rupture.

conditions, have obstruction to the superior vena cava. Varices of the lower end of the esophagus are common in association with cirrhosis of the liver and may also complicate thrombosis of the portal vein; sometimes cases of cirrhosis of the liver terminate fatally because of hemorrhage from rupture of the esophageal varices. In contradiction to our own experience, the varices of the lower end of the esophagus are also said to occur in connection with syphilitic cirrhosis of the liver (*hepar lobatum*). Hemorrhage from the esophagus may be due to abrasion from foreign bodies, ulcers, may occur in the various hemorrhagic diseases, and is often due to rupture of varices. Occasionally a thoracic aneurysm erodes into the esophagus with consequent fatal hemorrhage.

Corrosion of Esophagus.—This results from the ingestion of corrosive poisons such as the strong acids, phenol, and strong alkalies. Included in the last group is commercial lye which, in this country, is frequently the cause of corrosion (Clerf). The corrosive substances produce first an inflammation

followed rapidly by more or less extensive necrosis. In the less severe cases the necrosis may be limited to the crests of the longitudinal folds and points of narrowness of the esophagus. In more severe cases necrosis may be extensive and deep throughout the esophagus. In the event of recovery cicatricial stenosis follows the more severe corrosions.

Inflammations.—Acute catarrhal inflammation sometimes occurs as the result of ingestion of too hot or irritant food or drink, or it may extend from a catarrhal inflammation of the pharynx. In the more severe cases of thrush of the upper alimentary canal the process may extend into the esophagus. Acute fibrinous esophagitis, in which the exudate is usually deposited along the crests of the longitudinal folds, may complicate severe infectious diseases such as scarlatina, and typhoid fever, but true diphtheria of the organ is rare. Superficial streptococcus infections are likely to show moderate degrees of necrosis of the mucous membrane. The pustules of smallpox may be encountered in the esophagus. More extensive suppurative inflammation of the esophagus may extend from the pharynx or throat and may follow abrasion by foreign bodies or corrosive poisoning, because of the entrance of pyogenic organisms. This may be superficial or may extend in a dissecting manner for considerable distances under the mucosa, and may ultimately lead to a suppurative peri-esophagitis.

Chronic catarrhal inflammation may be due to prolonged passive hyperemia and to repeated irritation such as occurs in alcoholism. It also accompanies paralysis of the esophagus and the various forms of dilatation. There is thickening of the mucosa, sometimes with the formation of small polypoid outgrowths, varying degrees of atrophy of the muscle, and fibrosis. Chronic catarrh may also be accompanied by swelling of the glands, due either to mucinous degeneration or to obstruction of the duct, producing the so-called chronic follicular esophagitis. Leucoplakia is sometimes observed in the esophagus.

Infectious Granulomata.—Tuberculosis may extend from the larynx or pharynx. Hematogenous miliary tuberculosis is more apparent in the musculature than in the mucosa. Tuberculous ulcers may occur perhaps as the result of swallowing infectious sputa or due to lymphogenous transport from neighboring foci of tuberculosis. Tuberculosis of mediastinal lymph nodes may extend to the esophagus and produce tuberculous ulceration (Flexner, Cone). In syphilis there may be gummatous erosion of the esophagus. More significant, however, is the cicatricial stenosis or other alteration of form of the esophagus, due to contraction of scar tissue in the neighborhood of healed gummata. Actinomycosis is rare.

Cysts.—Congenital cysts usually are of relatively small size and occur in the lower third of the esophagus. They are often lined with ciliated columnar epithelium (Pappenheimer). They may be the result either of misplacement of lung anlage or failure of disappearance of embryonal esophageal tissue. Small retention cysts of the esophageal mucous glands may occur as the result of infection or may accompany chronic follicular esophagitis.

Tumors.—Papilloma, adenoma, fibroma, lipoma are not at all common and when they occur are likely to show somewhat elongated pedicles due to traction upon the tumor by swallowing. Leiomyoma (Tschlenow) and rhabdomyoma are also said to occur.

Cancer of the esophagus is fairly common, is most frequent in the fifth decade and attacks men more often than women. It usually occurs in the form of a ring encircling the esophagus, but may occasionally be confined to one side of the wall. It may sometimes be a dense firm scirrhus type of tumor with constriction due to connective tissue growth and a relatively small amount of superficial necrosis, or more commonly is a fungating growth extending from 2 to 10 cm. along the esophageal wall, projecting into the lumen in massive form and showing extensive necrosis. It is especially likely to occur at the points of normal narrowness of the esophagus, namely, opposite the cricoid, the bifurcation of the trachea, and at the cardiac orifice of the stomach. This suggests the etiological importance of repeated insults at these points. Cancer of the middle and lower third of the esophagus is distinctly more frequent than that of the upper third, and, although statistics vary, it appears that cancer of the lower third is the most common. Dysphagia depends apparently upon the actual obstructing influence of the cancer. Histologically, the tumor is usually a squamous epithelioma with extensive keratinization and pearl formation, but in some of the cases the keratinization is not marked and central necrosis of the epithelial masses is prominent. Occasionally, basal cell carcinoma is observed. Cylindrical cell carcinoma is rare but occurs more frequently in the lower third than in other parts. It may originate from the mucous glands and perhaps also from remnants of primary embryonal esophageal tissue.



FIG. 267—Eroding carcinoma of upper third of esophagus.

The esophageal cancer usually appears as a single growth, and only rarely are there secondary smaller growths in the esophagus due to lymphatic dissemination. In rare instances a carcinoma involving one side of the esophagus may show what appears to be an implantation of cancer upon the opposite side. Metastasis occurs to the lymph nodes both above and below the lesion,

but is more frequent and widespread in the latter situation, where it is especially likely to involve the nodes around the cardiac orifice of the stomach. Metastasis to the cervical lymph nodes is sometimes of importance in establishing a diagnosis. Metastasis to lungs and liver is not uncommon but more distant metastasis is unusual. The local extension of the tumor may result in perforation into the trachea, the bronchi or lungs, and occasionally into the pleural and pericardial sacs. Extension into the aorta may result in fatal hemorrhage. Involvement of the recurrent laryngeal nerve, either by direct extension or as the result of cancerous involvement of the mediastinal lymph nodes, may produce laryngeal paralysis.

Sarcoma is extremely rare, occurring especially in old age and the male sex, and attacking by preference the lower third of the esophagus. Grossly, it may be a submucous, nodular tumor or a flat diffuse tumor. Histologically, it may be a spindle cell sarcoma, a round cell sarcoma or even more rarely a lymphosarcoma.

Secondary tumors of the esophagus are unusual. Cancer may spread from the stomach by direct extension, and similarly from the pharynx and the thyroid gland. Sometimes it may extend into the esophagus from neighboring lymph nodes such as those of the mediastinum. Secondary sarcoma is even more rare than secondary carcinoma.

Alterations of Lumen.—Obstruction to the passage of food may be produced by the presence of foreign bodies, projecting tumors, or to a true stenosis of the wall, such as may be produced by scars following corrosion or such lesions as gumma. The lumen may also be narrowed by the presence of tumors within the wall and by various types of phlegmonous and other inflammations. Spasm of the esophagus may occur in any part of its wall but is most common at the cardiac end. Undoubtedly some of the cases of spasm are part of a psychoneurosis, but many cases have no such apparent origin, and except in rare instances where disease of the vagus nerve is found, the condition is without cause. The lumen may also be narrowed by compression from without, such as may be produced for example by thoracic tumors, thoracic aneurysms, and thyroid enlargement. Above points of obstruction there is likely to be primarily a hypertrophy of the musculature of the esophagus followed by local dilatation.

Dilatation.—This may affect the entire wall of the esophagus, either in a small part, or throughout the length of the tube, or it may be local in the form of diverticula. Rarely, the dilatation may be of congenital origin. As has been said, local dilatation, usually not very extensive, appears above points of stricture or spasm. The more extensive and larger dilatations are those which are sometimes called idiopathic and those which definitely accompany cardiospasm. The latter condition may progress without very definite symptomatology, and because of the fact that careful investigation of certain cases of idiopathic dilatation shows hypertrophy of the muscle of the lower part of the esophagus, it seems possible that the idiopathic cases are in reality due to cardiospasm. The fact that stimulation of the neighboring nerves produces

simultaneously relaxation of the esophagus and constriction of the sphincter, makes it probable that functional disturbances or organic lesions of the vagus nerves are of great importance in the cardiospasm and the accompanying esophageal dilatation. In other words, in those cases where cardiospasm exists, the presumptive associated atony of the esophageal muscle is probably important in permitting dilatation. The dilated esophagus in this condition may be so large as to have a capacity of a liter or more. The longitudinal folds are more or less obliterated and the mucosa shows a chronic catarrh. The musculature of the wall is scanty but whether this is simply attenuation or true atrophy is not certain. Hypertrophy of the circular muscle at the lower end of the esophagus and of the cardiac sphincter is often observed.

Diverticula may be traction diverticula or pulsion (pressure) diverticula. Traction diverticula are small and occur in the anterior or lateral walls near the bifurcation of the trachea. They are usually funnel-shaped and rarely exceed a depth of 5 or 10 mm. The condition is commonly due to the contraction of scar tissue in the mediastinal lymph nodes or other tissues of the mediastinum, which when adherent to the esophageal wall lead to traction and diverticulum formation. Pressure or pulsion diverticula, also sometimes called Zenker's diverticula, may occur in any part of the esophagus but are most common at the junction of esophagus and pharynx, and are therefore really esophagopharyngeal diverticula. The condition is commoner in advanced years and in the male sex. The dilatation is often saccular in character, may attain a diameter of several centimeters and may be so large that when filled with food it can compress the esophagus. The mucosa is usually thickened by a chronic catarrh and the muscle much attenuated or atrophic. The diverticulation is regarded as a sort of hernial projection of the lining of the esophageal wall between the fibers of the inferior constrictor of the pharynx. It is supposed that the increased effort in the first stage of deglutition, due to deformities of the mouth or swallowing of large pieces of food, may force the material upon this relatively weak part



FIG. 268.—Dilatation of esophagus probably due to cardiospasm. Chronic catarrhal esophagitis.

of the esophagus so as to produce local dilatation. The opening of the sac is in the posterior wall near the level of the cricoid cartilage, but when fairly large the sac itself is likely to project laterally and may be visible in the external surface of the neck.

STOMACH

Congenital Malformations.—Sometimes the vertical fetal position of the stomach is retained in after life. The stomach may also occupy an abnormal position in connection with hernia through the diaphragm, and in situs inversus viscerum. Congenital closure of the cardiac or pyloric orifice is usually a part of more general malformation. Congenital diverticula, sometimes combined with inclusion of such glandular structures as pancreas, may occur in any part of the stomach. It is doubtful that hourglass stomach is of congenital origin. Of great importance is congenital pyloric stenosis, sometimes called hypertrophic pyloric stenosis (see Sauer). There is little doubt that this is of congenital origin although symptoms usually are not observed until about two weeks after birth (Ladd). The condition is more frequent in the male sex and sometimes shows familial distribution. The most striking feature is marked thickening or hypertrophy of the muscular walls of the stomach, beginning at the pyloric orifice and extending for two or three centimeters along the pyloric canal (Sauer). There is sometimes fibrosis of the submucosa and in many cases the mucosa is thrown into longitudinal folds. The pyloric orifice is much reduced and often will barely admit a probe. The exact origin is doubtful. Some authors consider that it is primarily muscular and represents a tumor-like growth of the muscle in this situation. Others regard the muscle hypertrophy as secondary to spasm, which may be neurogenic, or due to faults of secretion leading to excessive contraction.

Postmortem Changes.—Not infrequently rigor mortis of the gastric muscle will cause ring-like or complete contraction of the circular bundles. These deformities, however, can easily be removed by a moderate amount of traction. Postmortem digestion of the stomach is extremely common and exhibits itself principally in the mucosa, at first along the cardiac end of the greater curvature and subsequently in other parts. The mucosa is soft and easily scraped off. Eventually the entire stomach wall may become involved and perforation may occur. The characteristic feature of these postmortem changes is that there is absolutely no reaction on the part of the tissues. Especially in connection with passive hyperemia of the stomach, postmortem digestion may lead to small extravasations of blood. The bacterial products of decomposition may act upon the blood pigment so as to produce a dark green, dark brown, or black discoloration referred to as pseudomelanosis.

Retrogressive Changes.—Cloudy swelling is not at all uncommon in the glands of the gastric mucosa, occurring in connection with catarrhal inflammation, passive hyperemia and the other general conditions which produce cloudy swelling. Fatty degeneration occurs under similar conditions and is especially marked in the infectious diseases, high grade anemias and phosphorus poisoning. Amyloid is likely to be found in the vessels, more particularly of the

submucosa and the mucosa. Russell's fuchsin bodies are said to be common in the mucosa and in the muscularis of nearly all adults and are increased in the chronic catarrhs. Hematogenous pigmentation is not uncommon in cases of chronic passive hyperemia. Calcification occurs particularly as calcium "metastases" in the vessels and in the tunica propria near the acid glands. Atrophy is likely to attack the glands or the muscle or both. Muscle atrophy is most apparent in the so-called chronic atrophic gastritis. Glandular atrophy occurs in the same condition and also appears in high grade anemias, especially pernicious anemia. The most significant functional change due to glandular atrophy is diminution or absence of gastric secretion, *achylia gastrica*.

Circulatory Disturbances.—Active hyperemia occurs physiologically in the course of digestion. Pathologically, it may be a simple acute hyperemia due to the irritant character of foods and drinks. It may be a part of acute inflammations of various types and is likely to accompany various forms of enteric fevers. Passive hyperemia is extremely common and accompanies chronic heart disease, chronic lung disease, cirrhosis of the liver, thrombosis of the portal vein and similar conditions. The hyperemia is usually present as a more or less diffuse reddening of the entire stomach, which after it has persisted for some time leads to a chronic catarrhal inflammation. Thus, the mucosa is likely to be thick, soft, red and covered with adherent viscid mucus. Histologically, there is cloudy swelling, fatty degeneration and mucinous degeneration of the glandular epithelium. The tunica propria is likely to be infiltrated with plasma cells, although this is difficult to determine positively, sometimes with polymorphonuclear leucocytes, and in more advanced stages there is fibrosis. Hematogenous pigmentation may be found in the tunica propria and in the submucosa; the latter also is fibrosed. Accompanying passive hyperemia there may be small petechiæ in the submucosa and the mucosa, especially of the fundus, which may ultimately result in the production of multiple hemorrhagic erosions. If varicosities of the veins be produced, severe hematemesis may occur from their rupture. Blood streaking and staining of vomitus secondary to the chronic catarrhs may be due apparently to leakage from overdistended capillaries. In general anemias the stomach is likely to be extremely pallid throughout and sometimes there is in addition fatty degeneration of the epithelium. The more severe chronic anemias, such as pernicious anemia, are frequently accompanied by atrophy of the mucous glands, sometimes in the form of chronic atrophic gastritis. Hemorrhage into the stomach may be the sequence of chronic passive hyperemia, hemorrhagic erosion, rupture of varices, erosion due to foreign bodies, and is of particular importance as an accompaniment of chronic ulcer and cancer of the stomach. It may also be of traumatic origin. Hemorrhage into the stomach may also be a sequence of abdominal operation and is more frequent where there is jaundice. As to whether such hemorrhages are traumatic in origin or due to other unknown cause, is not definitely settled. It is possible that such hemorrhages may be due to vascular thrombosis, which produces either infarcts or local pas-

sive hyperemia. In *melena neonatorum*, hematemesis may accompany the more common bloody diarrhea. The nature of this process remains unexplained.

Inflammations.—Acute catarrhal gastritis is believed to be extremely common although it is rarely observed at autopsy. It may apparently be caused by excess of food, food that is too hot or too cold, irritant foods and alcoholic drinks. The mucosa is the seat of active hyperemia, is swollen and covered with thick, sticky, glairy mucus. Histologically, the principle changes are hyperemia associated with cloudy swelling and mucinous degeneration of the epithelium. The tunica propria is normally so rich in round cells that it is difficult to say whether or not there is an additional infiltration of lymphoid cells. Acute fibrinous gastritis sometimes accompanies acute infectious dis-

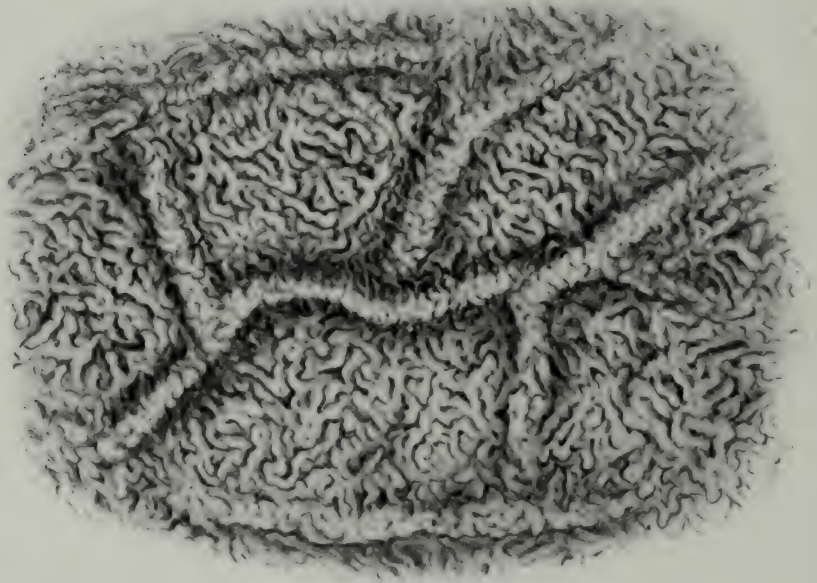


FIG. 269—Chronic hypertrophic gastritis showing thick folded mucosa.

eases and may be the cause of the more severe gastric disturbances in the course of these diseases. It is only rarely that a true diphtheria of the stomach occurs, secondary to involvement of the throat. Acute suppurative gastritis may occur in connection with pyemia and endocarditis, or as the result of infection of corrosive lesions. This is in the form of focalized abscesses in the wall of the stomach. Localized suppuration in the neighborhood of cancers and ulcers of the stomach may extend to produce an acute phlegmonous gastritis, as is true also of the erosions around foreign bodies. Suppurative lesions of the esophagus may extend into the stomach. Sometimes suppurations, as for example those in the lesser peritoneal cavity and in the pancreas or other neighboring organs, extend into the stomach.

Chronic gastritis may affect principally the mucosa and submucosa or involve the entire thickness of the stomach. The forms involving the mucosa are referred to as chronic hypertrophic gastritis and chronic atrophic gastritis.

Chronic hypertrophic gastritis may be due to chronic irritations similar to those which produce acute catarrhal gastritis; it may be due to retention of food in the stomach, such as may be caused by the scars of ulcers, obstructing influence of cancers, or constricting adhesions about the pyloric end of the stomach. The stomach may be of normal size or somewhat dilated. The rugæ are likely to be somewhat more prominent than normal and less easily flattened by stretching. The mucosa is definitely thickened, principally by proliferation of glandular epithelium. The swollen epithelial parts project between the ramifying connective tissue septa of the tunica propria so as to present to the naked eye a mosaic-like marking of the mucous membrane. Histologically, the glands are elongated, and in the neighborhood of the muscularis mucosæ, either coiled or sometimes bifurcated, resembling glands of Lieberkühn. Not infrequently goblet cells are encountered and sometimes the glandular lumen is filled with mucin. It is difficult to determine actual cell infiltration in the tunica propria, but in many cases a definite fibrosis can be made out, more particularly in the lines of depression of the mosaic-like marking. The muscularis mucosæ is sometimes the seat of hypertrophy and the submucosa may be fibrosed. Occasionally a moderate hypertrophy of the muscularis is observed. Fibrosis of the muscularis and of the serosa also occur. Sometimes proliferation of the epithelium appears to be of atypical character, but before such a diagnosis is made it is important to exclude the possibility of aberrant islands of intestinal glands, frequent in the stomach. Sometimes the hyperplasia of the glandular parts of the mucosa is excessive in various foci, so that there are projections of nodular character upon the mucous surface constituting the so-called verrucose catarrh or état mamelonné.

Chronic atrophic catarrhal gastritis may apparently be due to the same causes as chronic hypertrophic, may be a later stage of chronic hypertrophic or may accompany prolonged high grade anemias. In most cases the stomach is dilated. The mucosa is thin, pale, glossy and through it the vessels of the submucosa are clearly visible. The thinning affects all the coats and is accentuated by the variable degrees of dilatation of the stomach. Microscopically, the mucosa is found to be thin, and the glands short and well separated from one another. Cloudy swelling, fatty degeneration and mucoid degeneration occur in the glandular epithelium. The tunica propria is likely to be distinctly fibrosed. The muscularis mucosæ is thin and attenuated and the submucosa fibrosed. There is atrophy and attenuation of the muscularis of the stomach associated with moderate fibrosis of this coat and also of the serosa. Alcoholism is often regarded as an important cause of both forms of chronic gastritis, but according to Hirsch "chronic alcoholism alone is of doubtful etiological importance in causing chronic gastritis."

Chronic interstitial gastritis or chronic fibroplastic gastritis is not common, and is often difficult to distinguish from scirrhus carcinoma of the stomach. The causes of the condition are entirely unknown. It produces a form of stomach commonly referred to as "leather bottle" stomach. The organ is reduced in size and the wall considerably thickened, associated with marked

increase in density. The character of the mucosa varies in different cases, sometimes being hypertrophic and sometimes atrophic. The outstanding feature is a marked increase in thickness of the submucosa, which in cross sections is prominent, pale, pearly and glistening. Histologically, this may be the seat of a mature type of fibrosis, or may be fibroplastic in character. It is generally thought that the thickening and increased density of the submucosa leads to the muscular atrophy which is commonly present. There is associated fibrosis of the musculature and the serosa. In the cases reported by Armstrong and Oertel, the chronic fibrosis is of a somewhat granulomatous character, but there is no good reason for believing that the lesion is tuberculous or syphilitic in nature. It is possible, however, that general passive hyperemia may be the starting point for the fibrosis; and that circulatory change is present is indicated in some of the cases by the presence of an endarteritis. It is sometimes referred to as *linitis plastica*. In all cases careful distinction should be made between this form of disease and scirrhus cancer of the stomach.

Corrosion of Stomach.—The ingestion of corrosive poisons produces appearances in the stomach which vary with the character of the poison. Aschoff divides these into four different groups. The fixing corrosives include particularly phenol, mercuric chloride and formalin. These produce immediate death of the superficial parts of the stomach so that the cells are fixed in a solid, thick, firm but friable, pale or dark brown mass. In the less severe cases this affects the ridges of the rugæ but as a rule attacks the entire lining, fixing the mucosa and the prominent rugæ. Usually the patient dies almost immediately from shock. When death is not immediate, the tissue underneath the necrotic parts shows hyperemia, edema and inflammatory reaction. Histologically, the fixed cells show nuclear and cytoplasmic characters very much the same as with the ordinary types of fixation. The burning corrosives include especially sulphuric, hydrochloric and nitric acids. The superficial parts are discolored, soft, moist and necrotic, and can easily be scraped away. Sulphuric acid tends to char the tissue first yellow and then black, nitric acid stains yellow and dark brown, and hydrochloric acid pale yellow or white. Histologically, this material is completely necrotic, and the degree of the reactionary hyperemia, edema and acute inflammation varies with the length of life following the poisoning. The softening corrosives include the strong alkalies, particularly sodium hydrate, potassium hydrate, lysol and lye. In these cases the discoloration is not as great as in the preceding group and the softening of the necrotic material much more pronounced. The weak corrosives, including oxalic acid, chromic acid, arsenous acid and phosphorus, produce lesser degrees of superficial necrosis, and since death does not ensue so quickly, the reactionary hyperemia and inflammation are likely to be severe.

Infectious Granulomata.—Tuberculosis of the stomach is extremely uncommon. It may occur as miliary tuberculosis in the mucosa or submucosa, or there may be tuberculous follicular ulcers, usually in association with a similar process in the small intestines, in which case the involvement of the stomach is often due to retrograde transmission along the lymphatics. Occa-

sionally tuberculous abdominal lymph nodes erode into the stomach. It seems probable that the stomach possesses a certain amount of inherent resistance to tuberculous involvement such as, for example, is the case with the uterus. Although in the normal stomach the hydrochloric acid may be in sufficient concentration to inhibit growth of the tubercle bacilli, or to kill them, this does not apply in victims of tuberculosis because in many there is an associated reduction of hydrochloric acid of the stomach. Furthermore, although there are numerous lymphoid follicles in the gastric mucosa, yet these are apparently more resistant than similar follicles in other parts of the alimentary canal.

Syphilis attacks the stomach in the form of gumma, which may be single or multiple and usually occurs in the submucosa. Ulceration of the mucosa may accompany gumma formation, and it is at least conceivable that syphilitic endarteritis may be the basis of gastric ulcers of the peptic ulcer type. Distortion of the shape of the stomach secondary to healed gummata may produce such conditions as hourglass stomach or cicatricial stenosis of the pylorus. Diffuse fibrosis of the stomach associated with atrophy of the mucosa, due to syphilis, is unusual (Gatewood and Kolodny). Congenital syphilis may affect the stomach in the form of gummata or in the form of diffuse round cell infiltration of the various coats. Actinomycosis and anthrax occasionally occur but usually are secondary to lesions elsewhere. Of importance is the fact that diseases of the lymphatic system such as typhoid fever, Hodgkin's disease, and lymphosarcoma may manifest themselves in the stomach. They may remain simply as lymphoid hyperplasias of the follicles or occasionally ulcerate to produce single or multiple ulcers.

Ulcer of the Stomach.—Acute ulcers, which tend to heal, occur as the result of erosion of hyperplastic lymph follicles, may occur in infectious diseases without follicular hyperplasia, may be due to erosion of petechiae (hemorrhagic erosions) and may be due to erosion by foreign bodies (Schultze).

Peptic ulcer, round ulcer or simple gastric ulcer is peculiar in that it tends to persist and become chronic, heals slowly, if at all, and may exhibit several dangerous complications and sequels. Figures as to sex incidence vary. At autopsy it seems to be more frequent in males than females, but clinically, according to Martin, the reverse is true. Clinically, the average age for females is 27.1 years and for males is 36.6 years (Martin). The lesion is, however, common in more advanced life. Anemia and ulcer are frequent concomitants, but it is difficult to state that anemia predisposes, because hemorrhage from the ulcer may be the cause of the anemia. In animals, exhausting diseases (Ivy) and deficient diets (Pappenheimer and Larimore) appear to be of importance in originating the ulcer and in favoring its persistence. Gastritis, acute and chronic may predispose. Constitution, as studied by Draper, seems to have a place among predisposing causes. The neurotic temperament has not been proven to be of importance. Enteroptosis has no apparent influence (Gruber and Kratzeisen).

The ulcer is usually a single, round or oval, sometimes elongated elliptical,

loss of continuity, situated in the posterior wall of the pyloric portion of the stomach near the lesser curvature. The pyloric part of the stomach is sometimes referred to as the ulcer bearing area. Sometimes two or more ulcers occur. Gruber and Kratzeisen found only 6 per cent. in situations other than the ulcer bearing area. The diameter varies from a few millimeters to 2 to 3 cm. or more. Within a few weeks of its origin, the ulcer extends into the muscular coats, but has little disposition to extend widely in lateral diameter (Crohn, Weiskopf and Aschner). In the older ulcers the margins are indurated. The ulcer may be "punched out," or more commonly funnel shaped, often with "terraced" margins, the steps of the terrace representing smaller extent of destruction as the deeper coats are involved. Aschoff and also Stromayer find



FIG. 270.—Perforated peptic ulcer of pylorus, showing terraced edge.

the edges nearer the pyloric orifice flatter or less steep than the other margins, presumably because of the rubbing of the food as it passes through the narrower part of the stomach. The ulcer is covered, and partly filled in, by a granular or slimy, pale, bloody or brown tinged exudate, often digested or rubbed off in the autopsy specimen. Hyperemia is common around the margin and with the earlier ulcers may be widespread. Acute, or chronic hypertrophic gastritis are common but not constant. In the early stages the underlying serosa often shows a deposit of fibrinous exudate, which later is represented by thickening or more often fibrous adhesions to surrounding structures.

Microscopically, as pointed out by Askanazy, four layers can usually be identified, namely, of exudation, of fibrinous necrosis, of granulation and of cicatrization. The exudate occupies the ulcer and extends for a variable distance into the tissues. It may be purulent, fibrinopurulent, or occasionally catarrhal, and not infrequently shows hemorrhage. Eosinophiles are often

present but in the later stages lymphoid and plasma cells may predominate. The zone of necrosis is usually definite but may be very thin in old ulcers. In addition to the ordinary nuclear and cytoplasmic changes of necrosis, there are often hyaline masses which stain as does fibrin, but show no network, no nodules, no asters, to characterize it as fibrin. It is probably derived from necrotic connective tissue. Granulation tissue, variable in extent and not different from granulation elsewhere, appears early in the course of the ulcer and is usually still present in old chronic ulcers. Scar tissue appears at the base of older ulcers and extends into the muscular and serous coats.

In addition to the destruction of the coats of the stomach there are often lesions of blood vessels and nerves. Acute periarteritis, with perivascular infiltration of leucocytes, lymphoid and plasma cells, and acute arteritis with penetration of these cells into the vascular wall, are common in and about the earlier ulcers. The inflammations become chronic in association with the older ulcers. Endarteritis deformans and obliterans are common. These may be due to involvement of the intima of the arteritis, or much the same appearance may be due to thrombosis with organization and even canalization. Arteriosclerosis is frequently observed and may occur as a local process in young persons (Ophüls) but Askanazy points out that ulcer patients fifty to sixty years of age or more may show no sclerosis of the gastric vessels. The nerves are interrupted with the destruction of the stomach coats and may show acute or chronic neuritis or perineuritis. The interrupted nerve bundles may elongate and become coiled to produce masses closely resembling the amputation neuroma.

In addition to the destructive and inflammatory changes in the mucosa, there may be proliferation of epithelium upward to produce papilliform overhanging masses at the ulcer margin, or there may be growth downward along the edge and into the base of the ulcer. This downward proliferation must not be confused with tumor growth. Occasionally, the resistance of the ulcer base is so low that small dilatations or diverticula are formed.

When ulcers heal they do so by organization and consolidation of the defect with ingrowth and apposition of the mucosa and a complete or nearly complete regeneration of the mucosa (Ivy). Griffini and Vassale showed that new glands are formed, some of whose cells differentiate to form acid cells, the tunica propria multiplies and a new mucosa is formed. The scar tissue may contract, so that about the healed ulcer are radiating lines of retraction. Sometimes the cicatrization is more extensive, and if the ulcer be situated near the middle of the organ, contraction produces the "hourglass stomach." If it be in the pyloric region the contraction may produce pyloric stenosis.

The complications of especial importance are hemorrhage, perforation and development of cancer. Hemorrhage is so common as to be regarded as a symptom. There may be occasional small hemorrhages, repeated small hemorrhages, with secondary anemia, or severe large hemorrhages which may be fatal. In the extension of the ulcer, larger blood vessels may be eroded laterally. Protective thrombi may be loosely formed or may be dislodged by peristalsis, gastric distention or by increase of blood pressure. Small hemor-

rhages may be due to hyperemia or to rupture of vessels in the granulation tissue.

The deep penetration of ulcers may lead to perforation and peritonitis of the lesser or greater cavities. This occurred in 20 per cent. of the autopsies of Gruber and Kratzeisen, but is probably less frequent in the clinically recognized cases. The fibrous adhesion of the stomach to neighboring structures tends to prevent peritonitis, even though the erosion of the ulcer often exposes pancreas or liver, or leads to the establishment of gastro-intestinal fistulæ.

There is no doubt that cancer follows peptic ulcer of the stomach, but there are various estimates as to how often this occurs. Wilson and MacCarty reported that 71 per cent. of peptic ulcers show cancerous change, but it is possible that many of the epithelial changes which they regard as malignant,

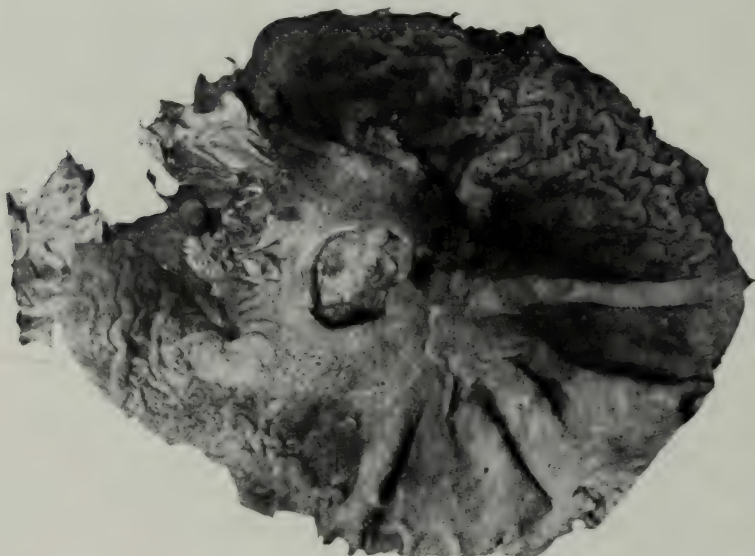


FIG. 271—Chronic peptic ulcer showing radiating retraction lines and in the base small nodules of early cancer. There is associated chronic hypertrophic gastritis.

would be considered inflammatory hyperplasia by others. MacCarty subsequently stated that all ulcers which exceed a diameter of 25 mm. show cancer, but this is not always true. Ewing found that only 5 per cent. of ulcers show cancer. The infrequency of cancer is also emphasized by Gruber. Clinically, Smithies and also Moynihan found that a large percentage of cancer cases give a history indicative of preceding ulcer, but this view is not supported by the studies of Friedenwald and of Taylor and Miller. When a cancer becomes a large cauliflower or eroding mass it is impossible to say upon pathological examination that it was preceded by ulcer. Clinically, interpretation of the history is difficult because the early symptoms may have been due to the cancer itself. Our own view is that the incidence of cancer in peptic ulcer does not exceed 10 per cent. and is probably close to the figure given by Ewing.

The pathological physiology of ulcer deals especially with gastric secretion and motility. It was long thought that hyperacidity is frequent in ulcer patients,

but Hewlett states that only one-half the cases show any indication of increased acidity, and Carlson found that the acidity is not materially different from that of normal stomachs. Hyperperistalsis is frequent both clinically and experimentally, but this does not necessarily mean rapidity of emptying. Two-thirds of Smithies' cases showed delayed emptying. Ivy found that hypermotility is due to intrinsic nervous mechanism, augmented by the extrinsic system. Local spasm is extremely common as revealed by radioscopic examination, and is probably of the same nature. The cause of pain is the subject of much discussion (see Ortmayer) and it is difficult to state whether it is due to inflammatory involvement of nerves, to spasm or other cause.

The exciting cause of gastric ulcer has been the subject of much clinical, anatomical and experimental study (see Karsner) and will be discussed in relation to faults of secretion, vascular lesions, parasites, neuromuscular influences, organs of internal secretion, cytolytics, and ferments.

Although no constant alteration of acidity is found in patients with peptic ulcer, it is possible that at the time of origin of the ulcer there may have been hyperacidity. By anastomosis of stomach and small intestine, so that unneutralized gastric juice impinges directly upon the intestinal mucosa, Mann observed the production of peptic ulcers of the intestine which tend to become chronic. As Matthes has shown, the intestinal mucosa is more susceptible to the deleterious action of hydrochloric acid than is the gastric mucosa, and it is doubtful that Mann's studies are applicable to the stomach unless there be heterotypic inclusions of intestinal mucosa in the stomach. Such inclusions, however, are probably not so frequent as gastric ulcer, and the histologic examination of a large number of ulcers has in our experience shown nothing to suggest heterotopia of this kind. Ivy and his collaborators have produced ulcer by Roentgen irradiation which coincidentally depresses secretion. It is therefore doubtful that hyperacidity is essential to the onset of ulcer.

Stasis of gastric contents has been shown by Bolton, by Friedman and Hamburger, by Ivy and others, to induce persistence of the ulcer. Bolton considers this to be due to the general irritability of the gastric contents. The obstruction, however, may lead to hyperperistalsis, and Sweet and his collaborators take the view that the traction of hyperperistaltic muscle upon the margins of the ulcer delays healing. Ivy has demonstrated that manipulation of an ulcer in an exposed pouch delays healing. Hyperacidity might dispose to persistence of the ulcer by producing hyperperistalsis, but hyperperistalsis can occur without hyperacidity. Thus, it may be said that hyperacidity is not necessary either to the origin or the persistence of peptic ulcer.

The conical shape of gastric ulcer with the apex toward the serous surface suggests that it is due to infarction, but the same form could easily be due to destruction so that the mucous coat is more extensively involved than the submucosa and more resistant muscularis. As shown by Litten and by Ivy, bland embolism does not produce infarction in the stomach. Cohnheim, by the intravascular injection of lead chromate, and Payr, by the injection of alcohol and of formalin, produced infarcts, but in these experiments there is added to the

occlusion of the arteries an associated direct destruction of tissue. Although the vascular supply of the pyloric portion of the stomach is poorer than that of the fundus (Berlet), infarction is rare in the human stomach, is usually massive (Baumann), and occurs only when additional vascular lesions reduce the normally rich anastomosis. The result of an infective embolus is to be regarded as an abscess. Those diseases, such as endocarditis and aortic thrombosis, in which bland embolism is common, rarely are complicated by gastric ulcer, and equally rare are stomach abscess in association with pyemia or septicemia. Acute and chronic arteritis and endarteritis are common in the neighborhood of gastric ulcer, but it is probable that they are secondary to the lesion rather than the cause of it. Arteriosclerosis is common, but even though it may be local in the stomach of young persons (Ophüls), it is not usually a severe disease at the average age of ulcer incidence and is sometimes absent in older victims of ulcer (Askanazy).

Various micro-organisms have been found in gastric ulcer but interest centers about moulds and bacteria. Moulds are common and Askanazy reports the production of ulcer by their injection. Hartwich and also Kratzeisen regard the moulds as saprophytes or symbiotes which merely tend to delay healing, but Kirsch and Stahnke were unable to establish this view experimentally. Turck's report that feeding of colon bacilli produces ulcer has not been confirmed. Rosenow maintains that gastric ulcer is due to hematogenous transport to the stomach of anhemolytic streptococci, and is supported in this view by Haden and many others. Contradictory reports were published by McMeans and by Celler and Thalheimer. Rosenow isolated streptococci from supposed portals of entry and from ulcers, and by injection of these strains intravenously in rabbits observed ulcer in 60 per cent. of the animals. Holman points out the difficulty of obtaining streptococci in pure culture and also their common non-experimental occurrence in laboratory animals. In order to establish the hypothesis of Rosenow, it would seem to be essential to be absolutely sure of pure cultures, preferably from the ulcer itself rather than from atria of infection, to work with animals in which the non-experimental incidence of the suspected organisms is low, to produce ulcers almost constantly, and to recover an organism which can be identified as that which was injected.

It has been suggested that spasm of arteries or of muscularis mucosæ might cause ischemia and consequent ulcer (von Bergmann). The occurrence of acute and chronic neuritis might be thought to be responsible for the spasm, but these lesions are probably secondary rather than primary. Durante reported that ligation and section of the splanchnics is followed by gastric ulcer, but this was not found to be true by Ivy or by Moladaja and Egoroff. Bedarida injected neurin, which paralyzes motor nerve terminals, directly into the stomach wall, and produced ulcer; but this same result follows the injection of so many substances that the effect cannot be definitely ascribed to the paralyzing action. Although the theory of neuromuscular influences in the production of gastric ulcer is of great interest (see Aschoff), it has not yet been clearly established.

The work of Biedl, of Friedman, of Mann and others suggests the influence of ductless glands or their secretions, especially the adrenal and the thyroid. The studies of the relationship of disturbances of ductless glands, whether they are supposed to operate directly or through the intermediation of the autonomic nervous system, have not been sufficiently correlated to permit of satisfactory conclusions.

Bolton has produced gastric ulcer by the injection of a cytolytic immune serum prepared by immunizing heterologous species against an emulsion of cells of the mucosa. In order for this to be applicable to man, it will be necessary to prepare sera by immunization not only of homologous species but of the same animal from which the gastric cells are secured. In other words there must be produced not merely an isogastrolysin but an autogastrolysin.

Kohler has offered the hypothesis that a deficiency of antipepsin in the body predisposes to peptic ulcer by removing the resistance offered by that antiferment against autodigestion of the mucosa, but Orator was unable to confirm this supposition in a study of fifty cases.

In summary, it may be said that pathologically, peptic ulcer is an inflammatory lesion so situated that gastric juice probably emphasizes the destruction of tissue. That the inflammation is primary is suggested but not proven. Various predisposing causes seem to be operative in the patients, but these are not conclusively established. The direct exciting cause of the ulcer has not been disclosed in such fashion as to be beyond doubt. The persistence or chronicity of the ulcer depends upon a variety of factors, none of which can be said to operate in all cases. Probably several of these factors act coincidentally. Thus, there must be considered especially, hyperacidity, stasis of neuromuscular or obstructive origin, the irritative and traumatic influence of gastric contents and the traction of muscle about the ulcer.

Tumors of the Stomach.—Benign tumors of clinical significance are not common but may be of importance and may produce marked obstruction to the pyloric outlet. The epithelial benign tumors include particularly the papilloma and the adenoma, which may be polypoid in character. Polypoid outgrowth may occur in connection with chronic gastritis, especially the hypertrophic form, but even without this preëxisting catarrh, multiple polypoid growths may be encountered. The papilloma may be distinctly pedunculated or sessile, and is made up of a more or less intricate papillary outgrowth of connective tissue of the submucosa, sometimes also with cells from the muscularis mucosæ, covered by cylindrical epithelium, occasionally with gland formation. The adenoma, whether of pedunculated or sessile form, is made up principally of glandular spaces showing variable degrees of irregularity and cell proliferation and supported upon a tissue closely resembling tunica propria. Only occasionally do the papillomata or the adenomata attain any considerable size. Not infrequently they show some digestion of the apex of the projection. Such tumors may become malignant but such an outcome is distinctly unusual. The subject of benign tumors is well reviewed by Douglas. Fibroma of the stomach may appear in the submucosa or in the subserosa and

more rarely in the muscularis. Occurring in the submucosa, the tumor may project into the stomach as a polypoid growth covered by cylindrical epithelium. Lipoma may be multiple but is usually small and of little significance. Myoma, fibromyoma, neurofibroma, lymphangioma and hemangioma of the stomach have also been described.

Malignant tumors of the stomach include sarcoma and carcinoma, the former being unusual and the latter very frequent. Sarcoma occurs principally in the fifth decade of life and about equally in the two sexes. It apparently originates more commonly from the submucosa than from other coats of the stomach. It may be a diffuse flat type of growth or a nodular projecting growth, sometimes pedunculated. The firm cut surface is homogeneous, gray and

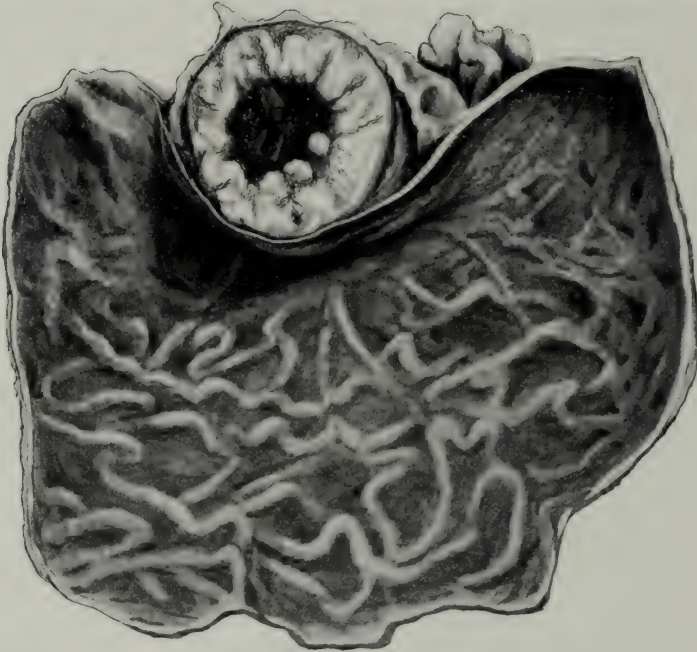


FIG. 272—Fibroma in wall of stomach.

fairly well vascularized. Sarcoma may appear in any part of the stomach but is more common in the pylorus and in the greater curvature. Goldstein found that of 592 sarcomas of the intestinal canal, 265 occurred in the stomach. Douglas estimates that sarcoma constitutes about 1 per cent. of all tumors of the stomach. Round cell sarcoma is by far the most common and it is probable that many cases so classified are in reality lymphosarcoma which, as pointed out by Broders and Mahle, is occasionally primary in the stomach. Much more rare are spindle cell sarcoma, fibrosarcoma, and myxosarcoma. Metastasis, except in the case of lymphosarcoma, is likely to be limited to the lymph nodes in the neighborhood and to the liver as in Thatcher's case.

Carcinoma.—Carcinoma of the stomach is extremely common, constituting according to various statistics between 20 and 40 per cent. of all malignant tumors of the body (Ewing). It is more common in men than in women and

the majority of cases occur after fifty years of age, although its occurrence earlier in life is by no means rare (Golob). It runs its course in about two years although some cases terminate sooner and others last ten years or more. The digestive disturbances are due principally to obstruction of the passage of food through the pylorus. Pain is by no means a constant feature. Vomiting is likely to occur several hours after the ingestion of a meal and may be blood stained or distinctly hemorrhagic. Occasionally, fragments of the tumor may be identified in the vomitus. There is usually absence of free hydrochloric acid and a considerable amount of lactic acid, but these features are by no means constant. Anemia is due in many cases to inanition but may be due to hemor-



Fig. 273—Cross section of carcinoma of pylorus, showing invasion through muscular coat. Army Medical Museum 17381.

rhage. Sometimes the features of the anemia closely resemble those of pernicious anemia.

Cancer may originate from the glandular epithelium or much more rarely from the surface epithelium, and may be derived from epithelial polyps or adenomata, and from atypical epithelial growth such as occurs in ulcers and their scars. A few cases can be referred to embryonal rests in the stomach.

Grossly, it is possible to distinguish soft or medullary carcinoma and hard or scirrhus carcinoma. All the forms are most frequent in the lesser curvature near the pylorus, but it is of interest to note that only rarely does cancer extend beyond the pyloric fold into the duodenum. The soft cancers, which include particularly adenocarcinoma and carcinoma simplex, may be well localized and nodular in character, or more especially with the carcinoma simplex, may

occasionally be diffuse. These soft cancers usually project into the stomach and show more or less marked ulceration. The tumor may be a cauliflower-like projecting mass, may be a more or less circumscribed ulcerating mass, may be distinctly focalized or extend in ring form completely around the pyloric end of the stomach. Beginning in the mucosa it rapidly extends into the submucosa and the muscularis, and involving the serosa may show localized extension along the serous surface or may be complicated by perforation. Not infrequently, owing to the slow course of the process, protective adhesions are formed around the margins of the point of perforation. Rarely secondary small nodules, due to lymphatic transport rather than to implantation, appear in the submucosa in the immediate neighborhood of the primary tumor. Superficial ulceration is almost constant and there may be extensive necrosis of the tumor growth with the production of a large ulcer. Sometimes saprophytes gain entrance and the necrotic mass becomes gangrenous. Secondary changes in the stomach depend in large part upon the retention of food. There is usually primarily a hypertrophy of the stomach followed ultimately by dilatation. The mucosa shows catarrhal inflammation, chronic in character, sometimes hypertrophic and sometimes atrophic.

Histologically, three chief forms are distinguished, the adenocarcinoma, the carcinoma simplex and the scirrhus carcinoma. The adenocarcinoma is likely to show great variation in the number of lining cells. Infiltration of the tissue is likely to be extensive, but the degree of reactionary inflammation depends in part at least upon the degree of ulceration. If the latter be extensive, there is likely to be a considerable infiltration of polymorphonuclear leucocytes, and in the more long standing cases granulation tissue may constitute a considerable part of the tumor mass. In occasional cases the adenocarcinoma is of mucinous type, which gives to the tumor grossly the typical gelatinous character. Carcinoma simplex shows islands of relatively undifferentiated epithelium invading the tissues, and showing reactionary inflammation depending in large part upon the degree of ulceration. This type of growth is somewhat more commonly diffuse than is the adenocarcinoma. Here again, depending upon ulceration, there may be a considerable growth of granulation tissue.

The scirrhus carcinoma of the stomach is almost invariably diffuse in type, beginning in the pyloric end of the stomach and extending in variable degrees toward the cardia. Here, there is thickening of all the coats, more especially the submucosa, due to the cancer, and of the muscularis in part because of cancer and in part because of hypertrophy. The stomach is small, of the "leather-bottle" type, and resembles very closely the stomach of chronic interstitial gastritis. Ulceration may occur in scirrhus carcinoma but is by no means a constant or necessary part of the picture. The final diagnosis usually rests upon microscopic examination.

Metastasis of gastric carcinoma is much more common with the soft forms than with the scirrhus forms. Metastasis of the soft forms is frequent and early in the lymph nodes of the immediate neighborhood. From these there

may be more or less widespread extension into the peritoneum, which may be thickly studded with small or large metastases. In our own experience metastatic involvement of the omentum, apparently as a retrograde extension, has been more common from cancer of the cardia than from cancer of the pylorus. Metastasis to the liver is extremely common and it is probable that this is very largely due to lymphatic dissemination. Nevertheless, it is probable that in certain cases, if not in many, the tumor invades blood vessels and is transported to the liver through the portal veins. The nodules in the liver may be few and small or may be numerous and large, so that the liver is often markedly increased in size. It is unusual, however, for the liver to show marked alteration of function. Metastasis to the bony system is much more frequent than is commonly supposed. Widespread carcinomatosis is not frequent.

Secondary tumors of the stomach are not common. Squamous epithelioma of the lower end of the esophagus may extend into the cardiac end of the stomach and appear as if it were primary in the cardia. Sometimes in cases of esophageal carcinoma small nodules are found in other parts of the stomach. Some suppose these to be due to implantation but they are more probably due to lymphatic dissemination. Kaufmann mentions metastases from breast, rectum and bronchial cancers.

Alterations of Form and Position.—Some of these have been mentioned, as for example, the reduction in size in chronic interstitial gastritis and the various stenoses or constrictions. Dilatation of the stomach may be acute or chronic. Acute dilatation may occur at any time as a result of pyloric stenosis, may be due to overloading of the stomach or to paralytic ileus of the duodenum. In addition, as pointed out by Hewlett, rare cases occur, in which the direct etiology is obscure, as for example, those which follow abdominal section or other operations, those which occur during the course of acute infectious diseases, particularly pneumonia, or during the course of chronic wasting and nervous diseases, and those which follow traumatic injury or occur in the midst of apparently perfect health. Clinically, there is vomiting, "abdominal pain, distention and tenderness," marked thirst and scanty urine, followed by collapse and death. Chronic dilatation occurs in chronic atrophic gastritis and chronic obstruction at the pylorus. Vomiting occurs usually two or more hours after eating. The vomitus shows reduced hydrochloric acid, sarcinæ, yeasts, bacteria and undigested food. Fermentation or putrefaction produce variable quantities of lactic acid, butyric acid and even acetic acid. Gases such as hydrogen, carbon dioxide, and rarely marsh gas may lead to marked distention. Gas produced postmortem, frequently causes moderate distension of stomach and intestines. The pathologic forms may show enormous distention, so that the greater curvature reaches the pubis.

Diverticula may form between the bands of scarring around old gastric ulcers or may be produced by traction of external adhesions.

In addition to the congenital abnormalities of position already mentioned, ptosis of the stomach occurs. This is usually in connection with ptosis of other organs, especially the transverse colon. It is commonly associated with faulty

posture (Osgood). The greater curvature may be nearly down to the pubis, but the stomach is only moderately or not at all dilated.

Foreign Bodies.—Various foreign bodies are swallowed by accident or by design, and may accumulate in great quantity and variety in the stomach. They may be passed through the intestinal canal, may remain in the stomach or perforate. Hair balls, masses of swallowed hairs, are seen in the stomachs of cattle and cats, and in man occur occasionally in the stomachs of mental defectives. As they increase in size they conform to the outline of the stomach and produce abdominal swelling. Often symptomless, they may cause stasis, ulceration and even perforation. Other substances may accumulate in much the same fashion (Hart).

INTESTINES

Congenital Abnormalities.—The intestines may be entirely or partly absent owing to congenital defects, more particularly when there is general malformation of the body. The intestine may be shorter than normal, more especially the large intestine. Occasionally, the appendix may be aplastic or completely absent.

Congenital atresias may occur in any part of the gut but are found especially in the duodenum, at the ileocecal junction and at the lower end of the large intestine. As a rule, the intestine above the point of constriction is dilated, filled with amniotic fluid or meconium and sometimes distinctly hypertrophic. The intestine below is usually collapsed and may be aplastic. Of great importance are those atresias which occur in and about the rectum. Three chief forms are observed. In one the rectum reaches as far as the anus but does not communicate with it. In another, the point of atresia is slightly above the anal orifice so that there is a blind anal groove extending up a centimeter or more. In the more serious forms the rectum ends blindly a considerable distance from the anus and there is no anal groove. These atresias at the lower end of the gut may communicate by fistulous tracts either internally with the vagina in females or the bladder or urethra in males or externally in the midline of the perineum. Although these fistulæ may be congenital in origin, it seems more likely that most of them are pathological in nature and due to the pressure of the contents of the obstructed intestine. There are in addition true congenital fistulæ about the lower end of the abdomen due to failure of development of the cloaca.

Dilatation occurs above congenital atresias as has been noted. These are, however, in a sense acquired rather than strictly congenital. The most important congenital dilatation is that which is spoken of as *megacolon congenitum*, or *Hirschsprung's disease* (Finney, Graves, Bartle). In this condition the colon throughout its entire length is moderately or enormously dilated, usually with elongation and with secondary hypertrophy of the muscular part of the wall. It is not incompatible with life and the patient may reach mature years, suffering only from retention of feces so that bowel movements are infrequent, sometimes separated by a week or more, associated with considerable abdominal enlargement. The most important congenital diverticulum is that referred

to as *Meckel's diverticulum*, due to incomplete regression of the omphalo-mesenteric duct. It usually occurs from 80 to 100 cm. above the ileocecal junction, projects from the convex surface of the gut as a pouch of about the same diameter as the gut, several centimeters in length, either blunt or rounded at the extremity and sometimes attached to the umbilicus by a fibrous cord. It is often of no significance, but may constitute part of the contents of a hernial sac, or may be the seat of inflammation extending from other parts of the gut. Inflammation may simulate appendicitis clinically. The tip may contain aberrant glandular tissue, particularly pancreatic in type, from which



FIG. 274—Meckel diverticulum of small intestine.

tumors may originate. Smaller congenital diverticula may arise in other parts of the intestine.

For convenience *acquired diverticula* are referred to here. These are projections of mucosa, covered with little or no muscle, through the muscular coat on the peritoneal surface near the mesenteric attachment, or into the mesentery. In the large intestine they project either into the peritoneum near the mesocolon or into the mesocolon. They are usually multiple, generally spherical and rarely exceed a diameter of 5 or 6 mm. They may be symptomless or may be the seat of inflammation, acute or chronic, generally called diverticulitis. This may lead to local peritonitis, which may become general in the event of rupture of a diverticulum. Diverticula without any muscle in the wall are sometimes referred to as false diverticula (Hervestine).

Congenital alterations of position of the intestine are exhibited principally in the form of transposition of the viscera and in the form of hernias. A *hernia* is a protrusion of part of the intestine or of other abdominal organs, associated with exvagination of the peritoneum, through some part of the abdominal wall. This may be through some such orifice as the inguinal canal or an incomplete union of the abdominal wall at the position of the umbilicus, etc. Hernias may be classified as external when they project on the outer surface of the body, or internal when they project into other parts of the body cavity. Thus, the external hernias may be inguinal, crural or femoral, perineal, umbilical, or abdominal (projecting through the linea alba). These may be due to increase or inadequate closure of orifices, or may occur as the result of excess strain upon orifices, which although apparently properly closed exhibit congenital weakness. They may be truly acquired as the result of traumatic interruption of continuity of the abdominal wall. As the result of improper or incomplete repair of the abdominal wall in surgical operations, the scar may subsequently stretch owing to pressure within the abdominal cavity, and hernia occur through the scar. Internal hernias include those which occur through the diaphragm; they may be congenital, or, if acquired, are of traumatic origin. Internal hernia may also occur into retroperitoneal spaces, more particularly that which exists at the point where the duodenum becomes a peritoneal organ. Covering the abdominal contents in the case of external hernias are the peritoneum, various fascias, muscle remnants, skin, etc., completely described in the textbooks on surgery.

Ordinarily, the contents of the hernia may readily be pressed back into the abdomen and the hernia is said to be reducible. Adhesion to the wall of the sac or the hernial ring may render the hernia irreducible. Adhesions between coils of gut or folds of omentum may result in the formation of a tumor-like mass reducible or not, depending upon adhesions to the sac wall. The accumulation of intestinal contents in coils of gut in the hernia may obstruct the intestine and the hernia is said to be incarcerated. The hernia is strangulated when, either as the result of incarceration or otherwise, the circulation of blood is obstructed, with consequent blood stasis, edema, hemorrhage, or necrosis and gangrene. Even without gangrene mild degrees of acute fibrinous peritonitis occur. Gangrene leads to local acute peritonitis, which, especially when perforation occurs, may become generalized.

Intussusception.—This term indicates the invagination of an upper segment of gut within a lower segment. This may be of small intestine into small intestine, small intestine usually with cecum into large intestine, large intestine into large intestine, or rectum externally through the anus as prolapsus recti. The outer sheath of the lower part of gut, the ensheathing layer, is called the intussusciens. The two layers of upper segment which are folded upon each other within the sheath constitute the intussusceptum. Except in prolapsus recti, intussusception usually gives rise to intestinal obstruction. The peristaltic action of the intussusciens exerts a pull upon the intussusceptum which is finally halted in its downward passage by the mesen-

teric attachment. Since the vascular supply and drainage of the intussusceptum are within the mesentery, there is interruption first of venous drainage and then of arterial supply. There follows blood stasis and edema of the intussusceptum which further interferes with circulation. Infection of the enclosed wall is followed by local peritonitis and consequent fixation of the intussusceptum. Finally, necrosis and gangrene with all the dangers and sequences of perforation, occur. Intussusception is more common in children than adults. Postmortem or agonal intussusception is distinguished by lack of local peritonitis and ready reducibility. This is also more common in children than in adults. It is common in laboratory animals, especially guinea pigs and rabbits.

Volvulus.—This term indicates a twisting of a coil of gut or a twisting in the long axis. The former is more common and is especially likely to occur in the sigmoid flexure. The mesosigmoid may be congenitally long or elongated by traction of adhesions, so that the sigmoid is a long, more or less angulated loop. Twisting on the axis of the mesosigmoid may bring the basal segments in contact so that they mutually press upon one another, become obstructed and strangulated. Similar volvulus may occur at the ileocecal junction due to long mesocecum. Volvulus of the small intestine is less common. Spiral twisting upon the long axis of the gut is unusual and is more often observed in the small intestine. Torsion, with secondary hyperemia, hemorrhage, edema, necrosis and sometimes infection may affect the omentum or epiploic appendages.

Intestinal Obstruction.—This is usually classified as mechanical and dynamic or paralytic. The former is due to conditions which physically obstruct the lumen such as hernial incarceration and strangulation, obstruction by fibrous adhesions, intussusception, volvulus, obstructing bodies such as swallowed foreign bodies, gall stones, inspissated masses of feces, tumors of the gut, tumors or similar masses compressing the gut, strictures of congenital or acquired origin, the latter usually inflammatory in character. Paralytic obstruction is due to acute peritonitis or to infarction of the gut. It may also be due to abdominal operations, extra-abdominal colics such as that due to renal calculus, infectious diseases such as pneumonia which probably operate through toxic products of the disease, and nervous diseases affecting spinal cord and sympathetic system.

Symptoms and signs such as abdominal distention and pain, hyperperistalsis above the point of mechanical obstruction, diminishing as distention of the gut increases, retention of intestinal contents and vomiting which ultimately becomes fecal, vary with the type, location and completeness of the obstruction. Finally a shock-like condition develops and death supervenes. The symptoms are more severe when the obstruction is high in the small intestine than when it affects the large intestine. The obstruction and associated symptoms are referred to as ileus.

The abdominal distention is due to filling of the intestine with solid, liquid and gaseous contents. The accumulation of gas may produce marked meteorism. This is primarily due either to accumulation above obstruction or in the

paralyzed gut, and is augmented by secondary circulatory effects due to the distention. The abdominal distention may be so great as to interfere with heart action, especially it seems by reducing flow through the abdominal veins and into the atria. The vomiting is due principally to accumulation of contents and may be contributed to by the intoxication and by reverse peristalsis. Pain is due principally to colicky contractions of gut segments and perhaps other factors.

When the obstruction is due to conditions in which there is a minimum of circulatory involvement, such as by foreign bodies, and pressure of adhesions, the symptoms and other manifestations are probably due to anhydremia (Foster and Hausler, Hartwell), the result principally of continued vomiting. The same condition is of unquestioned importance when the obstruction is due to volvulus, intussusception and other lesions which involve circulatory faults and necrosis of tissues. Ulcers may arise above the obstruction, due to overstretching and limitation of nutrition (Kocher), and may serve as a portal of entry for bacteria, but septicemia is rare in human cases and Hartwell and Houget show that it does not occur experimentally. That any toxic material is secreted by the intestinal wall is controverted by Dragstedt, Moorhead and Bureky, who were unable to produce symptoms by draining a closed intestinal loop into the peritoneum. Experiments dealing with toxemia are not finally conclusive. Whipple and his associates found that in animals with closed loops, but anastomosis so that intestinal flow is otherwise uninterrupted, death rapidly ensued. The reason for this is not clear. Whipple states that "nothing produced within the lumen of the intestinal tract can be directly concerned in the intoxication of intestinal obstruction." Rost points out that if poisons be present in obstruction, there is no satisfactory demonstration that they are not present in normal gut, and as noted above, drainage into the peritoneum shows no toxic effect. McLean could demonstrate no poisonous activity of the blood. That the pancreatic juice is effective as indicated by Sweet and his collaborators, as well as Davis and Stone, is not finally established. Nevertheless, a substance, poisonous upon injection, can be obtained from closed loops. It is not a true toxin, but probably a protein decomposition product. Whipple considered it a "proteose material" but Dale, because of the conditions of its formation and its effects, believed it to be histamine. This may be responsible for shock-like symptoms that sometimes occur. As pointed out by MacCallum, it is probable that the greater amounts of protein in the upper intestine account for the greater severity of symptoms of obstruction in the upper intestinal canal, where histamine may be produced in greater quantity than in the colon. Whipple found that the toxic material is not formed in colon loops.

Retrogressive Processes.—Chronic passive hyperemia may lead to hemosiderosis of the intestinal wall. The pigment of hemosiderosis may be in sufficiently large amounts to give a distinct light brown color to the mucosa. Melanosis is a dark brown or black pigmentation of the mucosa, which may affect the entire gut but is usually more prominent in or limited to the large intestine (Lignac). It does not usually affect the lymphoid structures or the glands. It appears as an amorphous granular pigment in the connective

tissue of the mucosa and does not respond to the tests for iron. Its chemical composition is not definitely known (Hueck). It occurs under a variety of circumstances of which constipation and wasting diseases seem to be important. Chronic inflammations may produce pigmentation, probably haematogenous, of the tips of the villi and in the neighborhood of the lymph follicles. Not infrequently dark brown pigmentation affects the lymph follicles, particularly those of the large intestine, where the pigmented points are so close together as to produce the so-called "shaven-beard" appearance. This is believed to be the late result of inflammation of a hemorrhagic character. Pseudomelanosis, such as affects the stomach, may also occur in the intestine as the result of action of hydrogen sulphide upon blood. The muscle of the gut may undergo atrophy, usually simple, but occasionally with a brown color, brown atrophy with relative or absolute increase in the muscle pigment. The glands may show cloudy swelling, mucinous degeneration, fatty degeneration, atrophy, etc., in connection with inflammations; and soon after death they show postmortem decomposition. Amyloid infiltration may affect the smaller vessels of any of the coats, and has been reported as occurring in nodular tumor-like form in the musculature (Askanazy).

Disturbance of Circulation.—Active hyperemia occurs physiologically during digestion and pathologically as the result of local irritation and acute inflammation. The redness of active hyperemia usually disappears soon after death. Passive hyperemia is common especially as the result of cardiac disease, disease of the liver, particularly cirrhosis, chronic disease of the lungs, thrombosis of the portal vein or vena cava, and may be observed locally in such conditions as intussusception, volvulus and incarcerated or strangulated hernia. Grossly, the intestine is likely to be somewhat thickened, of dark red or purple color, in the prolonged cases pigmented as noted above, and is likely to show catarrhal inflammation of the mucous membrane. Associated edema may be slight or marked and usually is most apparent in the submucosa. Submucosal hemorrhages are occasionally observed.

Varicose veins, incident to passive hyperemia are not common in the intestinal canal except around the anal orifice. Here the varicosities of the veins of the hemorrhoidal plexus constitute hemorrhoids. These frequently occur without any general passive hyperemia of the intestinal canal. There appears to be a familial tendency to development of the condition and apparently constipation is an important cause. In a few cases infection of the anus appears to be an etiological agent. The veins are elongated, tortuous and show fibrosis of the walls. The projection may be more prominent in the outer anal surface or in the lower end of the rectum just inside the anus. Thrombosis may occur and if followed by organization there may be shrinkage of the masses, or they may appear as tumor-like projections. Minor degrees of hemorrhage are common, especially where infection is present, and occasionally frequently repeated hemorrhages may lead to secondary anemia. Large hemorrhages rarely occur. In rare instances the thrombi may break down and lead to embolism in the lungs or liver.

Embolism in the arteries of the intestinal canal is not uncommon. The emboli arise from endocarditis, thrombi within the heart, thrombi upon diseased aorta or in other situations. Occasionally thrombosis appears to be primary in these vessels. The anastomosis of vessels in the rectum makes it improbable that minor occlusion is of any significance unless the embolus be infected. In the small intestines, and to a certain degree in the large intestines, in spite of fairly free anastomosis, occlusion of arteries usually leads to hemorrhagic infarct of the area supplied. If this be limited to the small area over the convexity of the gut, protective adhesion may prevent rupture into the general peritoneal cavity. If the embolus be infected, local suppuration may ensue rapidly. Obstruction of a larger branch means necrosis of a larger or smaller segment of the entire intestinal wall, which primarily interrupts the continuous flow of peristaltic movement producing ileus and secondarily leads to gangrene, rupture of the intestine and general peritonitis.

Hemorrhage from the intestinal canal may be small, large or even sufficient to be fatal. It may be due to hyperemia principally of the passive type, to infarction as indicated above, to acute inflammations, more particularly those which lead to necrosis of the mucosa, to ulcers such as gastric and duodenal ulcers and those of tuberculosis, syphilis and inflammations such as typhoid fever, which attack particularly the lymphoid structures of the intestines, and to tumors. Blood diseases, especially those with a hemorrhagic disposition, melena neonatorum, those infectious diseases which lead to hemorrhage elsewhere, foreign bodies and wounds from the outside, hemorrhoids, all may lead to hemorrhage. In the smaller hemorrhages the stools may be streaked with blood which, if the hemorrhage originate high in the intestine, is more or less digested, but if it originate near the anus is likely to be bright red. If the hemorrhage be large, the stools are likely to exhibit the so-called tarry appearance.

Inflammations.—Inflammations of the intestinal canal may be particularly prominent in one part or another, and are usually named more or less specifically as duodenitis, enteritis, appendicitis, typhlitis, colitis, sigmoiditis and proctitis. As a rule, it is usual to find some extension beyond the situation primarily indicated by the name. Thus, an inflammation of the colon is likely to show simultaneous involvement of the lower portion of the small intestine, and conversely any enteritis is likely to show a more or less extensive associated colitis. Acute catarrhal inflammation may be due to any of those causes indicated in discussing the catarrhs of the stomach, including various irritant foods and drink, as well as the irritation of decomposing or stagnant foods, irritant and escharotic poisons and those poisons generally grouped under the term "food poisoning" including products of the bacillus botulinus, bacillus enteritidis and the paratyphosus group. Grossly, the affected part of the intestine shows a soft, thick, red mucosa covered by viscid adherent mucus. The submucosa may be edematous. The muscularis shows little or no change. Histologically, there is mucinous degeneration of the epithelium and infiltration of lymphoid and plasma cells into the mucosa. More severe cases may show infiltration of polymorphonuclear leucocytes. Desquamation

of epithelium is a common feature both grossly and microscopically, and more particularly with catarrhal inflammation of the rectum and lower large intestine, the desquamation may be so active as to constitute tubular casts of the intestinal lining. In the more severe cases this is referred to as desquamative enteritis, colitis, or proctitis, as the case may be.

Acute follicular enteritis or enterocolitis is more common in children than in adults and may constitute the morphological basis of some of the forms of "summer complaint" of children. Accordingly, the lesions may be associated with dysentery bacilli, gas bacilli and other organisms. On the other hand, acute catarrhal enteritis or enterocolitis may be entirely independent of the more serious pathogenic organisms. The affected part of the intestines shows the appearances of catarrh and in addition hyperplasia of the solitary follicles, less marked in Peyer's patches. The follicles are swollen, fairly firm, pallid or hyperemic and project as small nodules into the intestinal lumen. As the disease progresses, these may undergo necrosis leading to the formation of small ulcers 1 or 2 mm. in diameter, often well-defined by reactive hyperemia in the neighborhood. This is spoken of as acute follicular ulcerative enteritis or enterocolitis.

Acute fibrinous inflammations of the intestine are well represented in bacillary dysentery, to be discussed subsequently. Acute fibrinous inflammation may also accompany acute infectious diseases, more particularly pyemia. Mercurial poisoning often shows an ulcerative and fibrinous inflammation of the lower ileum and upper part of the large intestine. A somewhat similar condition is sometimes observed in uremia. In fibrinous inflammation there is usually a profound catarrhal inflammation associated with considerable desquamation and deposit of fibrin upon the surface. Edema of the mucosa and submucosa is prominent, and microscopically there is likely to be a rich infiltration of polymorphonuclear leucocytes. Ulceration is a frequent accompaniment. Acute phlegmonous inflammation may follow the acute fibrinous forms, especially when ulceration occurs; or a more localized suppuration may be introduced through ulcers such as those of tuberculosis or cancer; and occasionally such an inflammation accompanies pyemia. Gangrene may also occur.

Chronic catarrhal inflammation of the intestine most commonly accompanies passive hyperemia due to chronic heart, lung, or liver disease. The mucosa is usually thickened, covered by viscid mucus and sometimes pigmented as noted under the heading of pigmentation. In cases of long duration, atrophy is sometimes seen, particularly in the mucosa, where there is shortening of the glands with wide interspaces of fibrosed tunica propria between them; and the atrophy may also involve the muscularis. In unusual cases the glands in chronic catarrhs of the intestine may show cystic dilatation producing a cystic type of chronic catarrhal inflammation. The formation of polypoid outgrowths in the course of chronic catarrhs of the intestine is much less common than in the stomach.

Gas cysts of the intestines, or intestinal pneumatosis, are uncommon. The lesion is due to the presence of gas or air in the lymphatics of the intestine and

mesentery, appearing as numerous bubbles in cysts whose walls are thin and transparent, tending to become thicker and more opaque as the result of granulation and organization. In most cases there is ulceration in the stomach or some other part of the intestinal canal, affording a portal of entry for air or intestinal gas, which if introduced under pressure such as may be produced by vomiting could infiltrate widely in the lymphatics. Masson suggests that the gas may be absorbed from the gut in solution and then liberated in the lymphatics. Hypotheses concerning bacterial or neoplastic origin of the gas have been offered, but our study of the literature (Mills) and of Sloan's case leads us to support the mechanical theory.

Special Infections.—Several infectious diseases have their most prominent pathological and clinical manifestations in connection with the intestinal canal. Although general manifestations are variable in the acute and chronic inflammations, they are of great significance in these special infections. These include particularly typhoid fever, bacillary dysentery, amebic dysentery and

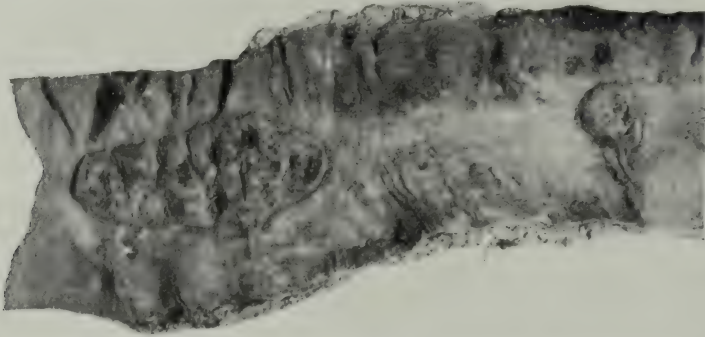


FIG. 275—Swelling of Peyer's patches in typhoid fever. Army Medical Museum 30456.

cholera. Infectious granulomata as they affect the intestines will be referred to in a separate section.

Typhoid Fever.—The nature of typhoid fever including its cause, character, mode of infection, gross and microscopic lesions, complications and secondary effects upon other organs have all been considered in the chapter on the principles of infectious diseases. It is important to regard typhoid fever as a general infection, with bacillus typhosus septicemia, and morphological manifestations, particularly in the lymphoid apparatus of the abdominal cavity. Its manifestations in the intestinal canal concern principally the lymphoid follicles of the small intestine, particularly Peyer's patches. The degree of involvement of the large intestine varies in individual cases. In occasional cases the lymphoid follicles of the stomach are involved. The small intestine is likely to show acute catarrhal inflammation in association with the changes in the Peyer's patches. In the Peyer's patches and to variable degrees in the solitary follicles, the first change is hyperemia. Following this there is acute hyperplasia of the lymphoid nodules. Thus, the patches are enlarged in all diameters and project into the intestine. The surface is likely to be convoluted so as to resemble

the brain of a small animal. In the later periods of this stage hyperemia is likely to be insignificant. Next comes necrosis of the lymphoid apparatus with desquamation of the necrotic material into the intestinal lumen, and the formation of an ulcer coextensive with the Peyer's patch. The ulcer shows elevated ragged margins and a somewhat roughened, necrotic, usually pallid base, not extending beneath the submucosa. Without secondary infection the further progress includes healing of this true typhoid ulcer by organization of the base and growth of surface epithelium. Glandular epithelium does not regenerate to any considerable degree, and it is probable that regeneration of lymphoid tissue is not extensive. Histologically, the stage of hyperplasia shows multi-

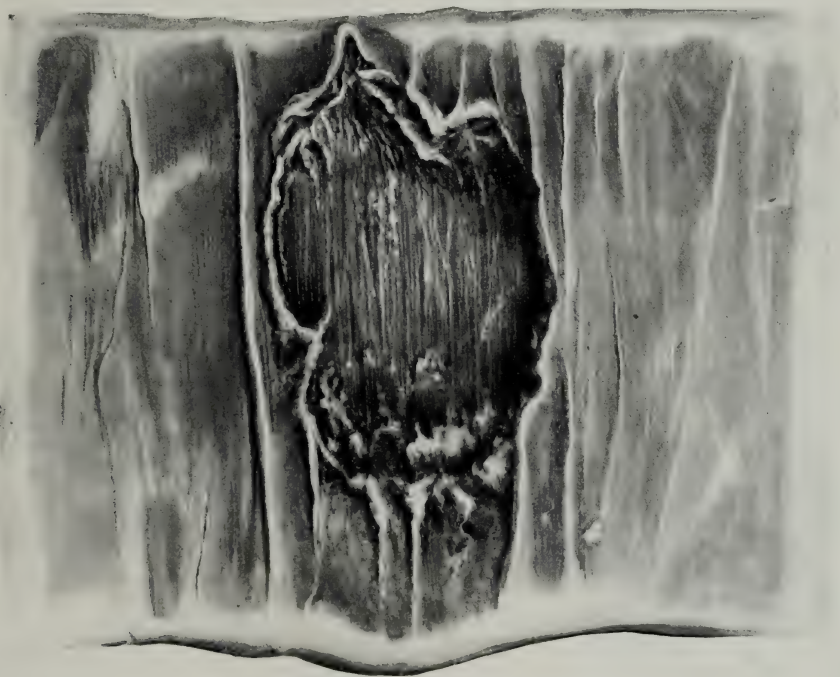


FIG. 276—Healing typhoid ulcer.

plication of lymphoid and endothelial cells, sometimes associated with slight infiltration of polymorphonuclear leucocytes. Early in the course, hyperemia is prominent but subsequently decreases. An important feature of the stage of hyperplasia is the phagocytic activity of the endothelial cells, which contain not only typhoid bacilli but also cell fragments, nuclear fragments and erythrocytes. In the stage of ulceration the remnants of hyperplastic lymphadenoid tissues are easily observed in the margins and the base, but, even without severe secondary infection, there is likely to be a moderate or marked infiltration of polymorphonuclear leucocytes under the necrotic material remaining in the ulcer. Granulation and epithelial regeneration are not markedly different from that occurring under other circumstances.

The surface of the typhoid ulcer may become secondarily infected and

hence extend deeply into the muscularis and even the serosa. Hemorrhage from incompletely thrombosed vessels or those from which thrombi may be dislodged by gaseous distention of the gut, may be severe or even fatal. Perforation into a space protected by adhesions may produce local abscess, and perforation into the peritoneal cavity a generalized acute suppurative peritonitis.

Other complications include degenerations in various viscera, catarrhal inflammations, notably of the respiratory tract, sometimes associated with broncho- or even lobar pneumonia and pleurisy, infections of the serous membranes by bacillus typhosus, particularly the meninges, focal necrosis of the liver, Zenker's hyaline necrosis of voluntary muscle, joint manifestations as the typhoid spine, and septicemia from secondary infections.

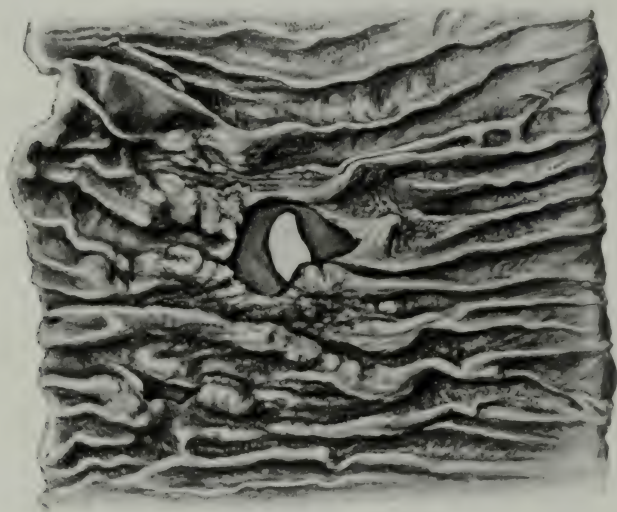


FIG 277—Perforated typhoid ulcer.

Infections by the paratyphoid bacilli are in general less severe as regards both general symptoms and local lesions.

The immune reactions, the carrier state, public health aspects of the disease and protection by vaccination, previously discussed, are all of great importance.

Bacillary Dysentery.—The term dysentery has been employed clinically to signify bloody and mucous diarrhea accompanied by straining and tenesmus, the stools as a rule being small and frequent. Pathologically, the term is restricted to two conditions with definite causes, the one, bacillary or epidemic dysentery and the other, amebic or tropical dysentery. In discussing bacillary dysentery no extensive references need be given, because they are all admirably covered in the article by Davison. The disease occurs in epidemic and in endemic form. It is observed particularly under conditions of crowding such as occur in asylums and in army camps. It constitutes one of the forms of summer diarrhea in children. It must be regarded as a specific infectious

disease which usually runs an acute course of six or seven weeks or may become chronic. It is due to two groups of organisms which are separated principally by the fermentation reaction with mannite and by agglutination tests with specific sera. The one which does not ferment mannite is the Shiga bacillus, also described by Kruse. Included in the mannite fermenters are the organisms now known as Flexner-Harris, Strong, and Hiss-Russell Y bacilli. They have certain differential features in regard to sugar fermentation and response to agglutinating sera, but these are not sufficiently constant for positive identification in all instances. Infections with the Shiga bacillus are usually more severe than those with other types, and this is probably due to the fact that the Shiga bacillus produces considerable quantities of toxins. These have been identified by Olitsky and Kligler as a thermolabile exotoxin acting upon the nervous system and a more stable endotoxin operating principally upon the intestinal canal. The mannite fermenters produce a less active endotoxin and little or no exotoxin. The organisms enter by the mouth and produce lesions in the large intestines associated with secondary toxic manifestations. They can be recovered from stools, particularly when cultures are made from small masses of bloody mucus, and can also be recovered after death directly from the mucous membrane. It is only rarely that they are found in the blood.

The intestinal lesions are confined almost entirely to the large intestine, although occasionally there is slight extension upward into the lower ileum, and sometimes



FIG. 278—Fibrinous exudate and ulceration in bacillary dysentery.

the appendix is involved. In the large intestine, the lower part and the rectum are likely to show the most severe inflammation. In the earlier stages the inflammation may apparently be simply a catarrhal inflammation, or pseudomembranous or even suppurative in character, but ulceration rapidly ensues. The ulcers are primarily in small foci but rapidly extend so as to involve a large part of the wall. They may be so extensive that only small islands of mucosa remain as red, swollen patches, sometimes covered with fibrin or with pus. The ulcers may extend only into the submucosa but not infrequently involve the muscularis. The edges may be sharp or may be markedly undermined. The base is usually of brown color due to hemogenous pigmentation. Histologically, the epithelium of the mucosa undergoes considerable necrosis early in the process, and may be surmounted by a network of fibrin enmeshing leucocytes and other inflammatory cells. The margins of the ulcer show an infiltration of polymorphonuclear leucocytes asso-

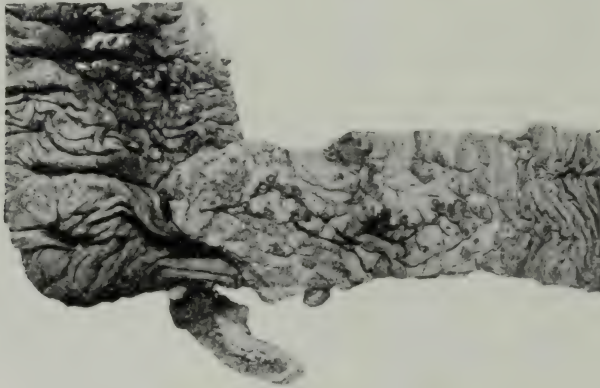


FIG. 279—Superficial necrosis of mucosa of lower ileum and cecum in bacillary dysentery. Army Medical Museum 6301.

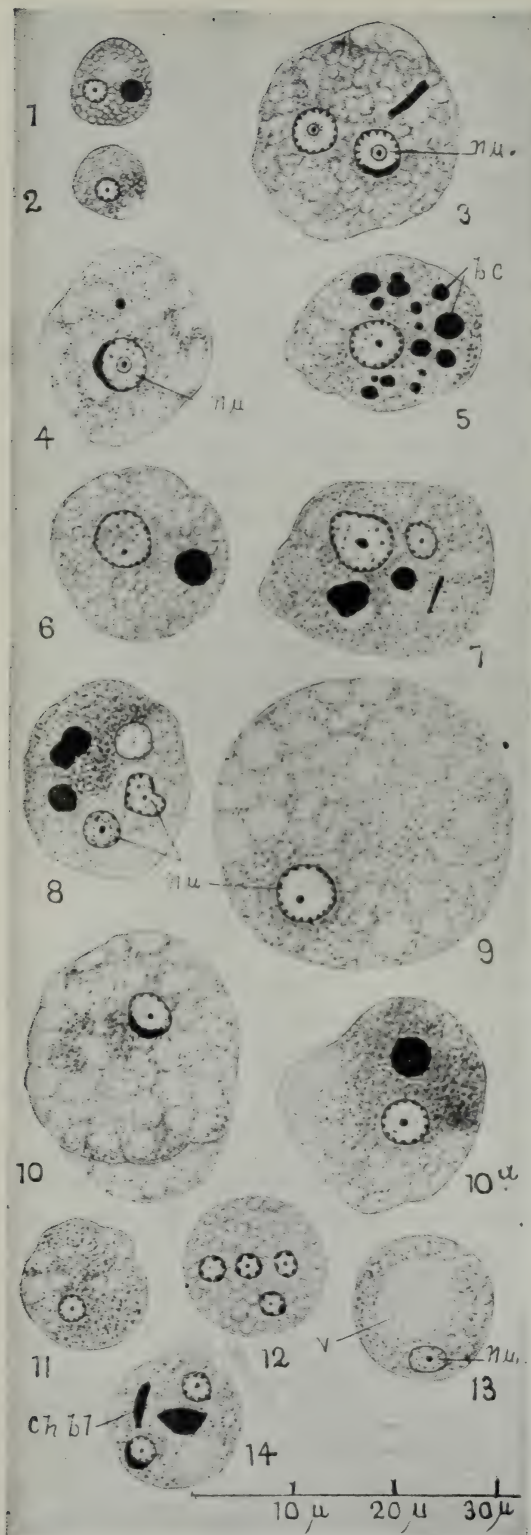
ciated with lymphoid cells, endothelial cells and sometimes eosinophiles. This inflammatory process also appears in lesser degrees throughout the intestinal coat and is commonly associated with inflammatory edema. As the disease progresses, reaction of the fixed connective tissue becomes apparent, with the production of granulation tissue, followed by greater or lesser degree of cicatrization. Epithelialization of the surface occurs from the remaining islands of living tissue. Secondary infection may play a prominent part, so that suppuration or phlegmonous inflammation of the gut wall occurs and, in occasional cases, a gangrenous type of inflammation is observed.

In severe cases the inflammation is so marked that the peritoneal coat is involved in a slight fibrinous exudate, which tends to produce adhesions. Perforation of the gut with general peritonitis is not common, since as a rule protective adhesions precede the perforation. Therefore, in case of perforation there is likely to be produced localized pericolic or perirectal abscess. The progress of the inflammation is such that massive hemorrhage from the ulcers is not common, because protective thrombosis is usually well established.

In contrast to amebic dysentery, which may produce large solitary abscess of the liver, bacillary dysentery only rarely produces abscess of the liver, and when observed, they are usually multiple. Acute inflammation sometimes leading to abscess formation may be observed in situations other than the liver, as for example, in the skeletal muscle and in the parotid gland. Acute endocarditis is not infrequent, but rarely severe, as is also true of myocarditis and pericarditis. The exotoxic manifestations in the nervous system are by no means constant and are principally in the form of peripheral neuritis. Non-suppurative inflammations of the joints are not uncommon and are believed to be due to the endotoxin absorbed from the intestines. Fortunately not very common, is the fact that after recovery the growth of connective tissue in the large intestine may undergo contraction, producing stricture at one or several points.

Although relapses occur, reinfections are unusual. During the course of the disease the patient develops specific agglutinins but usually not in titres higher than one to fifty. More especially in Shiga dysentery the use of therapeutic immune serum is of value. This is usually a polyvalent antitoxic serum. Prophylactic vaccination has not been widely employed because of the severity of local and general reaction due to the injection. It is likely that with the production of vaccines which do not produce such severe reactions, vaccination may be widely practiced, but there is no assurance that protection lasts more than a few months.

Amebic Dysentery.—This is also called endemic and tropical dysentery. It tends to be more chronic in course and less toxic than bacillary dysentery. Its major distribution is tropical and subtropical, but it also occurs in northern countries. It is much more common in adults than in children and may spread widely in asylums and in armies. It is due to *Entamoeba histolytica*, first described by Lösch in 1875, seen in liver abscess by Osler in 1890 and definitely related to the disease by Councilman and Lafleur in 1891. Walker's work was more conclusive in establishing the causative relation and has amply been supported by studies during the Great War. The student is especially referred to the works of Walker, Craig, Dobell and Wenyon and O'Connor. The organism is an actively motile ameba usually twenty to thirty micra in diameter, but sometimes measuring from eighteen to forty micra. In the fresh actively motile state the ectoplasm and endoplasm are not clearly defined, but as motility is reduced there still remains an active thrusting out of pseudopodia of almost entirely clear ectoplasm. The nucleus is vesicular and contains less chromatin than other intestinal amebæ. The cytoplasm may contain many erythrocytes or a few leucocytes or other cells but only rarely contains bacteria and intestinal debris, in contrast to the non-pathogenic *Entamoeba coli*. The organisms are recoverable in smears of the feces, especially from masses of mucus, and may be cultivated with difficulty. Tissue sections and inference from the observation of liver and brain abscesses indicate that it may gain access to the blood stream. The cysts are encountered in the feces during the disease, in carriers who have recovered from the disease and in those carriers who ingest, harbor and discharge the parasites without suffering from the



Figs. 1-8—*E. histolytica*, amoeba from the cultures. (1, 2) Small forms; (3, 7) Amoebæ, with two nuclei, one of which is smaller than the other; (5) amoebæ full of ingested blood corpuscles; (4) amoeba with large vacuoles; (8) three-nucleate amoeba.

Nu., Nucleus; b.c., blood corpuscles.

Figs. 9-11—*E. histolytica* from the ulcers of the large intestine of cats. (9, 10) Large vacuolate amoebæ; (10a) amoebæ showing pseudopodia. (11) Smaller, less vacuolated amoeba.

Figs. 12, 13, 14—Cysts from the cultures.

Nu., nucleus; v. vacuoles; ch. bl., chromatin block.

Fig. 14—Portion of large intestine of cat 1. Note the ulcerated areas. (Magnification, 3 diameters). From D. W. Cutler, Jour. Pathology.

disease. The cysts are thick walled spheroids with a maximum diameter of twenty micra, with clear cytoplasm and one, two, or four fairly dense nuclei; sometimes there is a glycogen globule but no other material in the cytoplasm. The disease is transferred by water, food and direct contact, and the organisms enter through the mouth. Introduction into the cat through the mouth or anus produces the disease. According to Kessel, feeding to rats produces a more chronic type of infection than occurs in cats.

The lesions of amebic dysentery are confined almost entirely to the large intestine. Although the disease is chronic in nature there may be clinically acute cases or exacerbations of the chronic cases. These, however, show no distinguishing features pathologically. In the early stages, there is an acute catarrh of the mucosa associated somewhat later with the appearance of small nodules with minute central ulcers. The ulcers tend to coalesce laterally along the valvulae conniventes. The ulcers may grow to considerable size and are usually disposed laterally in the gut. The outline is irregular and the edges are usually thick and elevated. Although not always the case, there is usually marked undermining of the edges with extension of numerous small fistulae under the mucosa. Deep extension of the ulcers is usually the result of secondary infection. The intervening mucosa may continue to be edematous, but only when secondarily infected shows fibrin formation or suppuration. The inflammation of the intestinal wall is



FIG. 281.—Thickening of gut and chronic ulcers in amebic dysentery.

of chronic character and as a consequence there is little or no localized fibrinous peritonitis or subsequent adhesion. The older cases usually show marked thickening of the intestinal wall due to fibrosis, but this is not invariably the case since in many instances there is actual thinning of the wall. Histologically, the earlier lesions show catarrhal inflammation with production of mucus. Penetration of the amebæ into the submucosa, apparently from the crypts, is accompanied by coagulation necrosis of the mucosa and submucosa, followed by liquefaction and ulceration. Cells which infiltrate in the neighborhood are principally lymphocytes, endothelial cells and a relatively small number of leucocytes. In these areas the amebæ can be identified as large cells whose nuclei are small, fairly dense and often polychromatic. The cytoplasm is not vacuolated but may contain red blood corpuscles, and an occasional leucocyte. In Malone's cases, secondary

infection and gangrene were common. Perforation, with acute generalized peritonitis and death, is more common in amebic than in bacillary dysentery, probably because of the failure of formation of protective adhesions in the former. The prominent sequel of amebic dysentery is the so-called abscess of the liver, usually fairly large and solitary, and occasionally multiple. The organisms are carried by the portal vein into the liver and set up there a coagulation necrosis followed by liquefaction, similar to that in the gut. Sometimes bacteria gain entrance with the amebæ and produce a true abscess. Without such infection the margin of the necrotic area shows an infiltration of lymphoid, plasma and endothelial cells and in the earlier stages a considerable number of amebæ. As time goes on, the connective tissue proliferates and encapsulates the area, or the process may extend to the surface of the liver and rupture. With extension of the necrotic mass upward, adhesions form between liver, diaphragm and lungs, so that perforation may occur into the lung followed by expectoration of brownish-red pus containing amebæ. In those occasional cases where spontaneous healing occurs, the content of the abscess becomes semisolid or gelatinous, and may ultimately disappear in the progressive growth of connective tissue and cicatrization. The occurrence of similar abscesses elsewhere in the body is extremely unusual.

Asiatic cholera is due to bacillus or vibrio cholerae or vibrio comma (Koch), and is transmitted particularly by water and food, occurring often as epidemic and in certain countries apparently endemic forms. The incubation period is approximately twenty-four to forty-eight hours and the disease is characterized in the milder cases simply by diarrhea. In more severe cases there are diarrhea, vomiting and prostration, and in the most severe cases these symptoms are accompanied by collapse, delirium, coma and death. The diarrhea is in the form of a large discharge of watery stools, the so-called "rice water" stools, the granules being principally bacterial masses, mucus and desquamated epithelium. Discharge of large quantities of water by rectum leads to dehydration, and this is commonly accompanied by anuria and acidosis. The pathological changes concern particularly the intestinal canal, but MacCallum calls attention to extreme rigor mortis, thick viscid blood, dryness of the serous cavities and enlarged thymus. It differs from most acute infectious diseases in that the spleen is usually not enlarged. There may be cholecystitis and cholangitis and in some cases small areas of bronchopneumonia. Other organs are likely to be normal, but the kidneys may be somewhat swollen and tense. The lesions in the intestinal canal are found particularly throughout the small intestines, but frequently involve also the large intestine and rarely may occur in the stomach. The intestinal content may be thin and watery or rather thick, turbid, and viscid. The intestinal mucosa may be smooth, somewhat pallid and translucent, or of pink color, covered with adherent mucus. There is moderate enlargement of the lymphoid apparatus of the intestinal canal, often showing in the center of the follicles a small opaque area of necrosis. In the lower part of the intestines there may be petechiæ. Hyperemia is present in the various coats of the intestine, involving not only the peritoneal

coat but also the mesentery. Sometimes the peritoneum contains a thick cloudy fluid which shows numerous desquamated mesothelial cells. Microscopically, in addition to general hyperemia, usually without any edema, there is necrosis and desquamation of the surface epithelium, acute hyperplasia of the lymphoid apparatus with necrosis in the centers of the follicles. Properly stained, the vibrios may be found in the mucus adherent to the surface and on the surface and in the intestinal crypts. The kidneys may show advanced cloudy swelling and even necrosis of the epithelium, and sometimes hyaline droplet formation in the tubular epithelial cells. The mesenteric lymph nodes are likely to be enlarged and soft, and microscopically show acute hyperplasia with necrosis.

The organisms are not recovered from the circulating blood but at autopsy may be recovered from the spleen. They are found in pneumonic areas as well as in the cholecystitis and cholangitis. The involvement of the mesenteric lymph nodes indicates lymphatic transmission, and the other conditions suggest, but do not positively prove, entrance of the organisms into the blood. The systemic manifestations are in part due to dehydration and in part to intoxication. Both pathologically and clinically the diagnosis depends essentially upon the recovery of the organisms. Rapid identification of the organisms is usually practiced either by the Pfeiffer bacteriolysis experiment or more particularly by agglutination. Immune bodies are produced in man as indicated especially by protection afforded by vaccination. The organisms usually disappear from the stools in the course of a few weeks, but the carrier state is observed and is believed to be due especially to infection of the biliary passages.

Infectious Granulomata. Tuberculosis.—Tuberculosis is the most frequent of the infectious granulomata in the intestinal canal. It may be primary or secondary. The primary form represents infection by milk or food and may be due either to bovine or human types of bacilli. The gross anatomical character is not essentially different from that of secondary tuberculosis to be described. If the lesions remain localized in the intestines or involve only neighboring lymph nodes, they may be regarded as presumably primary, but in the majority of cases wider extension occurs so that it becomes difficult to distinguish. The secondary form is usually due to chronic ulcerative tuberculosis of the lung and affects many of those who come to autopsy with the pulmonary disease. Although presumably due to direct infection by swallowed sputum, this type of lesion is more common in adults who expectorate than in children who do not. Occasionally the intestinal lesion is secondary to other forms of tuberculosis, as, for example, tuberculosis of the mesenteric lymph nodes and tuberculosis of the genito-urinary system. It affects principally the lymphoid follicles and Peyer's patches, and is more common in the lower end of the ileum from which it extends upward. It may also extend into the rectum and in unusual cases may involve the duodenum and even the stomach. The earliest change is the development of miliary or conglomerate tubercles in the follicles of the solitary nodes and of Peyer's patches. Following enlargement

and fusion, caseation occurs with subsequent ulceration of the surface. By the time ulceration occurs, there is usually a chronic catarrhal inflammation of the neighboring parts of the intestine. The ulcers tend to enlarge laterally because of the fact that the tuberculous process follows the intestinal lymphatics. It is not common for secondary infection to occur, but in some instances fusion of neighboring ulcers may produce an extensive area of ulceration extending for 20 cm. or more along the intestine, and in such cases there may be observed an acute pseudomembranous inflammation over the surface of the ulcer, or even gangrene.

Microscopically, the ulcer in the earlier stages is surrounded simply by a caseous mass with the usual marginal arrangement of endothelial and lymphoid cells. Outside this zone there is likely to be a subacute inflammatory reaction with infiltration of lymphoid, plasma and endothelial cells. In the neighborhood of the ulcer, more particularly in the submucosa and under the peritoneum, but sometimes also in the muscularis, there are often found miliary tubercles with small foci of central necrosis and with or without giant cells. When secondary infection becomes marked, the acute inflammatory reaction may entirely obliterate the characteristic features of tuberculosis. Tubercle bacilli are usually demonstrable microscopically unless the secondary infection is severe.

Characteristically, the ulcers are elliptical and so situated that their long axis is transverse to the long axis of the gut, but sometimes, more especially in the early lesions, they are circular or may even be coextensive with Peyer's patches. The ulcer is of generally elliptical or circular outline with an irregular margin and thick, elevated, undermined edges in which may be found small tubercles. The base of the ulcer is often cheesy, with small nodules representing tubercles, but with secondary infection the base may be stained brown by blood or show a moderate degree of suppuration. The most important diagnostic feature is the demonstration of tubercles in the peritoneal surface immediately underlying the ulcer. Often the tubercles occur in bead-like chains in the neighboring lymphatics. Depending in part upon the rapidity of the tuberculous process and in part upon the beginning of secondary infection, the peritoneum may show a deposit of fibrin, which in later stages may become organized and produce fibrous adhesions.

Under favorable circumstances the ulcer may heal by cicatrization and epithelialization. If the original ulcer were fairly extensive, cicatricial contraction may occur with the production of stenosis of the gut. Perforation of the intestine may occur, but the slow course usually leads to a preceding fibrous adhesion so that only local peritonitis or abscess formation results. Small hemorrhages, sufficient to be demonstrable microscopically in the stools or even to stain the stools grossly are not infrequent, but large fatal hemorrhages are distinctly unusual. Extension and perforation of ulcers near the anus in the lower part of the rectum produce perirectal "cold abscesses" which may rupture through the perineum and produce fistulae. The extension of the tuberculous process into the peritoneum may produce a widespread acute or chronic

peritonitis. Inasmuch as the ulcers are of chronic inflammatory character in the majority of cases, it is possible, although rarely reported, that the epithelium around the margin may proliferate to form cancer.

Syphilis.—Syphilis of the intestines may be either congenital or acquired. The congenital lesions are usually in association with lesions of the other viscera such as lung, liver, etc. The most definite lesion in the intestine, namely, small, flat, single or multiple gumma-like processes occur in the ileum although they may be found elsewhere. These may undergo ulceration as is true of the acquired lesions. In even more rare instances miliary gummata may be found in the gut. Lesions of the intestinal tract in acquired syphilis occur as gummata late in the disease. They affect particularly the rectum, the sigmoid and other flexures as well as other parts of the colon, but are rarely observed in the small intestine. The primary condition is apparently single or more rarely multiple gumma formation of the mucosa or submucosa, producing an elevated nodular tumor-like growth. The gumma breaks down to form an ulcer chronic in type and often extending transversely in the intestine. Histologically, the picture may be more or less obscured by secondary infection although the latter is not usually severe. There is the usual central necrotic mass surrounded by endothelial or lymphoid cells, in association usually with well marked chronic inflammation of both arteries and veins which may go on to actual occlusion. If perforation occur, the peritoneal infection is usually restricted because of preceding fibrous adhesions to neighboring structures. Of greater significance is the fact that since the gumma is a lesion which tends to undergo fibrosis, there may be cicatricial contraction and well marked stenosis of the intestine.

Actinomycosis affects most often the colon, in or near the cecum. There is found a more or less extensive deep ulcer with the small yellow actinomyces granules in the pus. Chronic adhesions of the neighborhood are common and the process extends through these to form fistulæ with neighboring coils of intestine, or other viscera, may produce acute generalized peritonitis, may invade the liver and other solid organs, or may penetrate through the diaphragm into the pleura and lung.

Lesions of Lymph Nodes of Intestines.—The lymph nodes, including both solitary follicles and Peyer's patches, may be involved as part of the general enlargement of the lymph nodes of the body incident to such diseases as lymphatic leucemia or its aleucemic form, and lymphosarcoma. Hodgkin's disease may similarly affect the intestines.

Ulcers of the Intestines.—These include ulcers due to various inflammatory diseases mentioned above, scybalous or stercoral ulcers and ulcers due to tumors benign and malignant. The peptic ulcer described above as it affects the stomach, also occurs in the duodenum and in the jejunum. *Duodenal ulcers* of this type are usually solitary but may be multiple. They are found as a rule in the first part of the duodenum upon the posterior wall. The ulcer is generally round, slightly terraced and of essentially the same general and microscopic character as that of the stomach (see MacCarty). Clinically, it

seems to be more common than ulcer of the stomach but postmortem statistics usually show it to be less so. Its cause is not known but perhaps the action of gastric juice has some important influence. It has a distinct tendency to heal and only rarely leads to the development of cancer. Peptic ulcers of the jejunum are rare except as a sequel of gastrojejunostomy. There is doubt as to whether the gastric juice causes this lesion, or whether it is due to trauma at the time of operation, or other cause.

Tumors.—Congenital tumors are unusual. Dermoid cysts occur especially in the small intestine, and we have observed one case of hemangio-endothelioma of the small intestine, probably of congenital origin. Benign tumors are not uncommon, especially lipoma and adenoma. Such tumors originate in the

mucosa or submucosa and, projecting into the lumen of the gut, may be exposed to the peristaltic action so as to become pedunculated, the pedicles sometimes being extremely long. Lipoma is particularly common in the colon but may be observed in other situations. It apparently arises in the submucosa and projects first as a lobulated nodule which subsequently becomes polypoid. Solitary tumors of this sort occur in the peritoneal coat, more especially in obese individuals. This must not be confused with the fat increase in the epiploic appendages which sometimes may be almost tumor-like in character. Adenoma may be single or multiple, and may grow as a papillary outgrowth, subsequently becoming pedunculated. It shows proliferation of the glands of the intestines. Occasionally, the number of adenomata may be so great as to con-

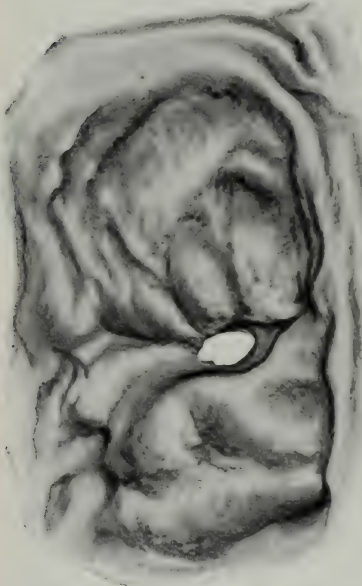


FIG. 282—Perforated duodenal ulcer.

stitute adenomatous polyposis of the intestine extending over a considerable length of the gut, but usually in the small intestine rather than in the large intestine. Such a condition may be primary or may follow an acute or chronic inflammation of the intestines. The polypoid tumors of the intestines may obstruct by their size or may produce intussusception by traction at the point of attachment. The adenomatous tumor may become carcinomatous either in a single tumor or in several tumors. Fibroma is rare except in the rectum where polypoid fibromata are sometimes encountered. This type of polyp and other polypoid tumors of the rectum may project externally through the anus. Myoma and fibromyoma, originating from the muscular layers of the gut, may be single or multiple but are extremely uncommon, as is true also of the adenomyoma. The hemangioma and lymphangioma are uncommon. The former is likely to be of cavernous type and as a group such tumors are disposed to be flat and infiltrate the walls of the intestine, producing obstruction by their

bulk rather than by the production of polypoid masses. The hemangioma may lead to hemorrhage. When neurofibromatosis occurs in the abdominal canal, it may affect the intestine, and apparently may occur in the intestine without widespread dissemination in the abdomen.

Of the malignant tumors, cancer is by far the most common. It is more frequent in males than in females and although it occurs in early life is most common in advanced years. The same types are observed in the intestines as in the stomach, but the scirrhus cancers are much less common and the mucinous cancers more common than in the stomach. The mucinous cancer is commoner in the large than in the small intestine. Cancer of the small intestine is particularly likely to affect the duodenum, although it may be observed in other parts. Cancer of the large intestine occurs in the cecum and in the flexures of the intestine, but cancer of the rectum is the most common cancer of the intestinal canal. The adenocarcinoma and the carcinoma simplex may occur as nodular masses or may be distributed in circular fashion around the gut. They tend to ulcerate early and may form large fungating masses. Obstruction may be produced by the size of the tumor or by the constriction of cicatricial tissue in its base. Such cicatricial contraction may be prominent in the occasional scirrhus cancers of the intestine. The mucinous cancer tends to form an infiltrating mass in the wall of the intestine, projecting sometimes in nodular form in the lumen, but not commonly producing the fungating masses seen in other types of intestinal cancer. Cancer of the rectum occurs particularly near the lower end of the rectum and in the vast majority of cases is a more or less projecting, ulcerated, bleeding, infiltrative adenocarcinoma which sometimes shows a considerable amount of mucus. Squamous epithelioma may occur at the anus. Cancers in any part of the intestinal canal may produce stenosis and sometimes perforate either into the neighboring organs or into the peritoneum. Small hemorrhages are common and occasionally large fatal hemorrhage occurs. The ulcerated tumors may be complicated by severe suppuration or by gangrene. Metastases occur into the neighboring peritoneum and lymph nodes and are commonly found in the liver. Subsequently, there may be widespread carcinoma of the peritoneum or a general carcinomatosis of the body.

The term *carcinoid* is applied to an irregular growth of epithelium seen most commonly in the appendix, but occasionally found in single or multiple forms in the small intestine. Grossly, the appendix may be somewhat enlarged and in the ileum there may be small nodular masses. Histologically, there are found in the submucosa, sometimes deeper in the walls, islands of epithelial cells usually fairly well circumscribed. That the epithelium is in abnormal position cannot be denied, but observation of such cases gives little reason for supposing that they are malignant. Rarely, however, in the appendix, somewhat similar tumors are observed, distinctly invasive and definitely malignant.

Sarcoma of the intestines is most frequently lymphosarcoma. It may be primary or secondary in the intestines. The multiple nodules of enlarged

infiltrating lymphoid tissue are most common in the ileum, sometimes are seen in the colon, but are rare in the duodenum. The circular, soft, reddish-gray projecting nodules, several millimeters or more in diameter, are often difficult to distinguish from other lymphoid enlargements in the intestines, but the involvement of other lymph nodes and the histologic appearance are usually adequate for diagnosis. The lesions may ulcerate and become the seat of suppuration. It is extremely rare for stenosis or intussusception to complicate this disease. Other forms of sarcoma although rare are more common in males than in females. Usually single, the sarcoma may be a circumscribed nodule or may extend in circular fashion around the gut. Only rarely is it polypoid. Histologically, round cell sarcoma is less rare than the spindle cell sarcoma. Except when the tumor microscopically is alveolated, it is extremely difficult to say that we do not deal with a solitary manifestation of a lympho-sarcoma. This type of tumor, as also the spindle cell sarcoma, is met with usually in the ileocecal region. We have observed one case of spindle cell sarcoma primary in the tip of a Meckel's diverticulum. Melanosarcoma is rarely observed in the rectum. It probably originates in the skin of the anus.

Secondary carcinoma of the intestine may be solitary but is more usually multiple. It may be a retrograde involvement through the lymphatics as the result of metastases in lymph nodes; it may be an implantation of cancer in the abdominal cavity, or may be secondary in close proximity to a primary cancer of the gut itself. Melanotic tumors, whether they be of the skin or of the choroid, more especially the former, are likely to show metastases in the intestinal canal. The wide dissemination of the various forms of sarcoma includes involvement of the intestines.

Parasites.—A wide variety of animal parasites may infest the intestine. These are discussed in the text books of protozoölogy. The tape worms do not produce significant pathological alterations of the intestine, but as has been indicated, the *dibothryiophyllum latum* may, because of absorption of its products, lead to profound anemia. Of the round worms, the larva of *trichinella spiralis* may be found in intestinal muscle. *Ascaris lumbricoides* may apparently cause ulcers of the lower gut, may constitute the nidus of intestinal concretions, or may accumulate in balls to obstruct the lumen. *Oxyuris vermicularis* and *tricocephalus dispar* are of little importance pathologically. *Anchylostoma duodenale* and *necator Americana* attach themselves to the mucosa of duodenum and upper ileum, and by their injury produce multiple small hemorrhages. The secondary anemia, either as the result of the hemorrhages or perhaps also of products of the worms, may be prolonged and severe and is usually accompanied by eosinophilia.

The flat worms may gain entrance to the body through the alimentary tract but do not lead to disease there. *Distomum hematobium* probably gains entrance through the skin. From the veins of the pelvis the worms may gain access to those of the rectum.

The most important pathogenic rhizopod is the *endameba histolytica*, the cause of amebic dysentery. The flagellates such as *lamblia intestinalis*, *tricho-*

monas intestinalis and subgroups, *tetramitus mesnili*, are found in the stools of patients with and without diarrhea, but their pathogenic significance is not established. The same is true of *blastocystitis hominis*. On the other hand, it is now found that *balantidium coli* may invade the mucosa of the intestine, principally the colon, and produce chronic inflammation and ulceration.

Foreign Bodies.—Swallowed foreign bodies of all characters may enter the intestine. Shellac, and various minerals administered as drugs may form intestinal concretions. Parasites, gall stones, hair and other swallowed foreign bodies, may be the nidus for calcified, sometimes laminated, hard or friable enteroliths. Masses of feces may by inspissation, sometimes associated with calcareous deposit, form concretions. All these are of importance as possible causes of obstruction, ulceration or perforation. Ordinary inspissated fecal masses, scybala, stagnant in cecum, flexures or diverticula of the colon, may produce chronic ulcers with more or less extensive non-specific granulation tissue, the so-called scybalous or stercoral ulcers.

Appendix.—Although in consideration of the intestinal canal there has been no sharp division of diseases of the different segments, the great clinical significance of the diseases of the appendix, more especially of inflammatory nature, justifies a brief separate discussion.

Acute Appendicitis.—Although this was suspected as a disease entity by others, it required the work of the late R. H. Fitz to establish its special identity. Numerous studies have been contributed by others, but the books of Kelly and Hurdon, of Deaver and of Aschoff are especially noteworthy. The milder manifestations of acute appendicitis affect principally the mucous membranes, and the more severe forms extend through the width of the wall of the appendix. Secondary inflammation may be due to extension of inflammation from the cecum as in typhoid fever, tuberculosis and dysentery. Inflammation may also extend from the female internal genitalia, particularly the Fallopian tubes, to the appendix. Infection may also be carried by the blood stream as in cases of septicemia and pyemia. It has also been suggested, although in our opinion not clearly proven, that cryptic infections such as those of the tonsils and of the teeth may be the entering point for bacteria with a particular affinity for the appendix. Although we speak of primary inflammations of the appendix, it is not clearly established that they do not originate in the cecum and thus invade the appendix, but, since the manifestations are so strikingly within the appendix and are cured by removal of that organ, this conception is practically acceptable. Formerly, much significance was attached to the presence in the appendix of various foreign bodies such as seeds of vegetables, concretions, usually fecal in character, metallic bodies and intestinal parasites, more especially *oxyuris vermicularis*. Although there is little doubt that these foreign bodies may readily be irritants and through ulceration of the mucous surface provide a portal of entry for bacteria, yet the great number of cases now operated upon because of increased diagnostic precision, shows that such foreign bodies are present in only a very small percentage of the cases of acute appendicitis. As with other parts of the intesti-

nal tract, the identification of pathogenic organisms is somewhat difficult. The vast majority of cases shows the presence of colon bacillus (Warren). A moderate number shows the presence of streptococci of various types and a small number shows the presence of a wide variety of other organisms. Admitting the possible fallibility of bacteriological methods under these circumstances, nevertheless, it seems apparent that from the bacteriological point of view, appendicitis is not a specific disease.

In *acute catarrhal appendicitis*, although the symptoms may be severe clinically, the appendix is likely to show relatively little gross morbid anatomical change other than slight swelling, moderate hyperemia, and thickening of the mucosa with accumulation of mucus upon its surface. Histologically, there is found cloudy swelling of the intestinal epithelium, marked accumulation of mucus,



FIG. 283—Appendix showing at one end acute catarrhal appendicitis with follicular hyperplasia, and at other end acute diffuse appendicitis with ulceration.

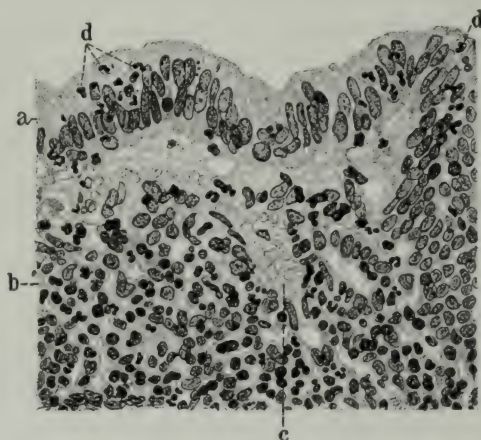


FIG. 284—Acute catarrhal appendicitis. The section shows a small portion of the surface epithelium (a) with part of a gland on the right-hand side, and the membrana propria (b) containing a dilated capillary (c). The epithelium and membrana propria are moderately infiltrated with polymorphonuclear leucocytes (d). From Kelly and Hurdon, *The Vermiform Appendix and Its Diseases*.

infiltration of lymphoid cells and polymorphonuclear leucocytes into the tunica propria and between the gland cells. Sometimes ulceration is present. In the submucosa the lymphoid tissue generally shows a slight infiltration of polymorphonuclear leucocytes. Except for the possibility of edema, the other coats are likely to show little change. As with catarrhal inflammation elsewhere, the mucous exudate may become purulent in character and may, either with or without ulceration, pass over into the diffuse form.

Acute diffuse appendicitis is definitely exudative in character and is disposed to become suppurative in type. Grossly, the appendix is usually swollen, markedly hyperemic and soft. The lumen may be filled with mucopurulent or

purulent material. Ulceration is distinctly more common than in the catarrhal form. The peritoneal surface may be covered with a thin film of fibrinous or fibrinopurulent exudate. Histologically, the milder cases show in addition to those features described in catarrhal appendicitis, considerable edema and exudation of polymorphonuclear leucocytes. The leucocytes may accumulate in masses to constitute small pockets of pus. The associated necrosis of tissue may lead to perforation of the appendix. When suppuration is pronounced the condition is often called *acute suppurative appendicitis*.

Acute gangrenous appendicitis may be due to invasion of saprophytic organisms through ulceration in some other form of appendicitis, or may be accounted for by vascular occlusion resulting from thrombosis infective in character, or from malposition of the organ. Grossly, the appendix is swollen, hyperemic, covered with fibrinous or fibrinopurulent exudate and shows brown or green discoloration in the areas of gangrene. These may be focalized near the tip, or in any other part of the organ, or may be diffuse. Histologically, the picture is much the same as in acute diffuse or suppurative appendicitis with areas of gangrenous necrosis.

The complications of acute appendicitis depend in certain measure upon the severity of the disease. With only moderate peritoneal involvement, as in the catarrhal and milder diffuse disease, the process may heal and the fibrinous peritonitis lead to more or less dense fibrous adhesions. Adhesions sufficiently extensive may produce partial or complete intestinal obstruction. If perforation occur after fibrinous or fibrous adhesions bind the organ to neighboring structures, there may be an inflammation limited to the area. If, however, these adhesions be broken through or have not been established, perforation produces an acute generalized peritonitis. Infective thrombosis of the appendiceal veins may extend to the portal vein and ascend to the liver, ultimately producing multiple abscesses. Occasional cases of septicemia or pyemia occur without extensive thrombosis. The drainage of the peritoneum toward the diaphragm probably accounts for the occurrence of subdiaphragmatic abscess and its sequels.

Chronic Appendicitis.—Chronic catarrhal appendicitis differs from the acute form in that there is relatively less swelling or hyperemia. Histologically, fibrosis may be present in the tunica propria and submucosa, and in these areas local histo-eosinophilia is likely to be more pronounced than in the acute form. Mucinous degeneration is prominent. It is difficult to say that chronic interstitial forms of appendicitis represent the progressive fibrosis of true chronic inflammation, or on the other hand, represent cicatrization of preceding acute



FIG. 285.—Involvement of appendix in typhoid fever showing typhoid ulcers.

attacks. The fact that such patients may show continued symptoms of low grade severity would point toward the process being inflammatory. On the other hand, the condition is found at autopsy in many patients who have reported no symptoms whatever. The atrophy of advanced life often shows the same morphology. The appendix is likely to be reduced in diameter and of firm consistence. The lumen may be narrowed or completely obliterated.

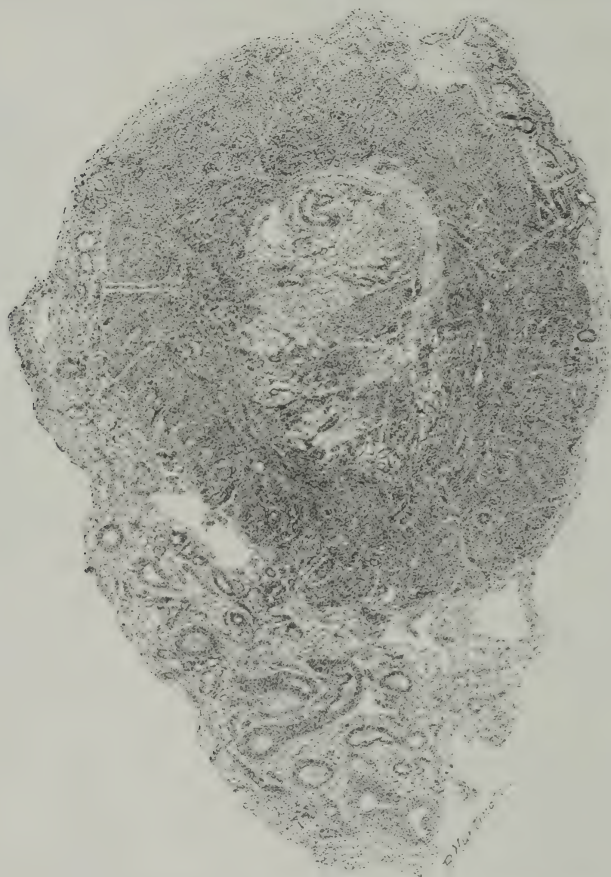


FIG. 286—Obliteration of appendix. The center consists of dense fibrous tissue containing a moderate amount of fat. The circular muscular coat is atrophic, the longitudinal layer well developed. The walls of the blood vessels in the mesappendix are somewhat sclerotic. From Kelly and Hurdon, *The Vermiform Appendix and Its Diseases*.

Histologically, fibrosis is found in all the coats, sometimes associated with atrophy of the muscularis. Between muscularis and submucosa there is often a considerable accumulation of fat. Associated with the fibrosis of submucosa, there is usually atrophy or partial disappearance of glands and of the lining epithelium. The lymphoid follicles and lymphoid tissue generally, are usually atrophic. This represents a partial obliteration of the lumen. In so-called chronic obliterative appendicitis which may also represent merely cicatrization, the same conditions are found except that the epithelium has usually com-

pletely disappeared. There is found a central mass of connective tissue surrounded by fat and then by fibrosed muscularis with or without atrophy.

Infectious Granulomata.—Tubercles may be found in the peritoneum of the appendix as a part of generalized tuberculous peritonitis. Tuberculous

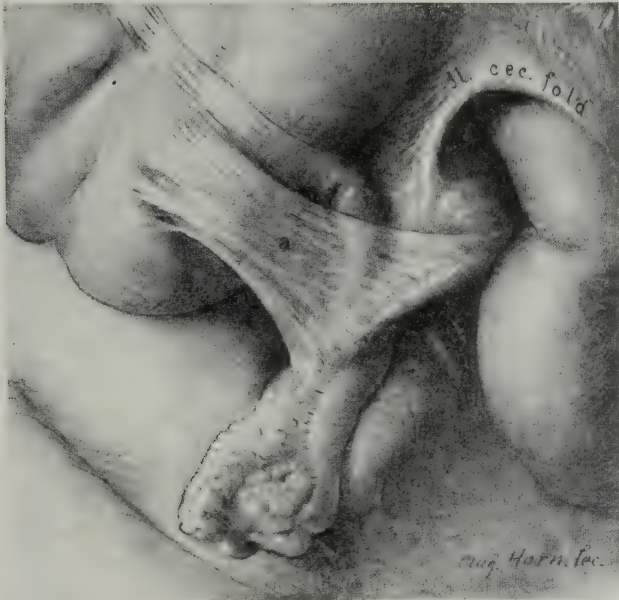


FIG. 287—Peritoneal adhesions about a chronically inflamed appendix.
From Kelly and Hurdon, *The Vermiform Appendix*.

involvement of the mucosa with ulceration is usually an extension from the same process in the intestine. Actinomycosis occurs in the appendix and suggests the possibility that the organisms may have been carried upon grains which lodge in the appendix.

Tumors of Appendix.—As has been mentioned, there is encountered not uncommonly in the appendix an irregular proliferation of epithelium into the submucosa and even the muscularis, usually in the form of more or less discrete islands of epithelium. This carcinoid shows no high degree of malignancy. Occasionally, however, cases are found in which the invasiveness of the epithelial growth is striking and the tumor is regarded as a true carcinoma. The appendix may be involved in metastases of other tumors, much as other parts of the intestine.

Foreign Bodies.—Various foreign bodies which may be swallowed may ultimately lodge in the appendix. It is probable that many foreign bodies, considered to be vegetable seeds, are merely concentrically laminated fecal concretions. The stagnant current of material in the appendix predisposes to the formation of small scybalous masses of feces which remain in situ. Except for *oxyuris vermicularis* intestinal parasites are not likely to occur in the appendix.



FIG. 288—Fecal concretion in appendix.

PERITONEUM

Congenital deformities are of little significance in the peritoneum, except where the folds which normally appear are accentuated or improperly formed so as to constitute fairly large bands in the peritoneal cavity. These are sometimes referred to as congenital adhesions but are simply faults of development. Their particular significance is that they may lead to strangulation of the intestines or other forms of intestinal obstruction.

Circulatory Disturbances.—Active hyperemia occurs in the early stages of acute peritonitis and may accompany inflammation of organs within the peritoneum. It is also likely to occur when there is sudden removal of pressure from within the peritoneum by withdrawal of large quantities of fluid. Passive hyperemia occurs as the result of chronic diseases of liver, lungs and heart, and as the result of the obstruction of outflow from the veins by thrombosis or from compression. Such passive hyperemia occasionally leads to hemorrhage, but its greatest importance is that it disturbs the drainage from the peritoneal cavity and results in accumulation of fluid, or ascites. Atrophic cirrhosis of the liver produces passive hyperemia in the portal circulation. The formation of peritoneal fluid is not seriously interfered with but its drainage is obstructed so that it may accumulate in extremely large quantities. Passive hyperemia as the result of heart disease is an important cause of ascites, but as a rule does not lead to such large accumulation of fluid as is true of atrophic cirrhosis of the liver. Chronic fibrosis of the lung and emphysema may also produce ascites. Compression of the portal veins or of the inferior vena cava by tumor masses, large lymph nodes and fibrous adhesions as well as thrombosis within the vessels, either the result of infectious thrombosis or of tumor thrombosis, may also produce ascites. Ascites must be regarded as an edema of the peritoneal cavity. The fluid is therefore thin, watery, colorless, of low specific gravity ranging between 1004 and 1015, with a low content of protein which rarely exceeds 3 per cent. Microscopically, there are found a few cells, usually of endothelial character, showing cloudy swelling or fatty degeneration, and a few leucocytes similarly degenerated. Ascites may also be observed under conditions where the edema may be more or less general, such as in chronic Bright's disease, nutritional edema, and the cachexias of malignant tumors. The serous exudate of tuberculous peritonitis and of involvement of the peritoneum by malignant tumors may closely resemble ascites. It is often difficult to distinguish an exudate of this sort and a true transudate such as characterizes ascites. Chronic fibrous peritonitis may produce ascites either generalized, or as localized saccules within the adhesions. Chyliform ascites is usually the result of obstruction to the thoracic duct such as occurs from malignant tumor invasion, tuberculosis and other diseases. Chronic peritonitis may also so obstruct the drainage from the lymphatics of the intestines as to lead to chyliform ascites. The fluid of ascites may sometimes be slightly milky because of degeneration of the cells which it contains. Ascites leads to dis-

comfort because of pressure of fluid and because of limitation of expansion of the thorax. If long continued it may lead to a chronic fibrous peritonitis.

Hemorrhage of the peritoneum may be due to direct trauma, such as by stab wounds and surgical operations, or may be due to indirect trauma, such as blows upon the abdomen with rupture of the internal viscera or vessels. Hemoperitoneum is not uncommonly caused by hemorrhage from the genital canal, particularly in females where it may be due to rupture of Graafian follicles, corpus luteum, or hemorrhage from extrauterine pregnancy. Hemorrhage may also be due to infarction, particularly of the intestine, rupture of aneurysms in the abdominal cavity, chronic passive hyperemia, tuberculosis of the peritoneum, hemorrhagic diseases, tumors of neighboring viscera and of the peritoneum.

Peritonitis.—Both acute and chronic forms may either be local or general. The localization of acute forms may be due to origin within a viscus, as the appendix, or to the presence of preëxisting limiting adhesions. Acute peritonitis may be due to chemical irritation such as the presence of bile, the fluid of ruptured cysts, prolonged ascites, and in the days of antiseptic surgery, was sometimes due to chemicals employed for antiseptis. This as a rule is an acute fibrinoseous peritonitis, but may become suppurative. Bacterial causes include streptococcus, staphylococcus, bacillus coli, pneumococcus, anaërobes, and particularly in local form around the female genitalia, the gonococcus. As the result of perforation of the gut, saprophytes may gain entrance and produce a gangrenous type of peritonitis. The acute inflammations of the peritoneum may arise as the result of extension by contiguity from inflammation within the intestines, within the uterus, particularly in puerperal sepsis, within the gall bladder, the urinary bladder, the pleura and other neighboring locations. In some instances the bacteria may precede or follow the extension of the inflammatory process. Extension of inflammation by continuity is best exemplified in extension of inflammation from the Fallopian tubes. Thus, gonococcal inflammation may extend directly through the fimbriated end into the peritoneum, but as a rule, leads only to a local peritonitis. If the primary tubal inflammation be streptococcal in type, a generalized peritonitis may occur. Of great importance are those forms of peritonitis due to perforation of viscera within or neighboring upon the peritoneum. Occasionally, acute peritonitis may be of hematogenous origin, accompanying a septicemia, especially in children, or a pyemia. In pyemia, it is likely that the peritonitis is due to the rupture of secondary abscesses of neighboring organs rather than direct invasion of the peritoneum. The acute inflammations of the peritoneum do not differ essentially from those of other serous membranes and may therefore be acute fibrinous, acute fibrinopurulent, acute suppurative, acute hemorrhagic and acute gangrenous.

Adhesions.—Adhesions are due to the organization of acute exudate upon neighboring surfaces of the peritoneum. Even with the most careful aseptic technique in surgery, the interruption of surface continuity results in a slight degree of fibrinous exudation, and as a consequence more or less extensive

adhesions are almost constant following surgical operation in the peritoneum. Of course, the smaller the amount of trauma, the less extensive the adhesions. Inflammations of appendix and gall bladder, inflammatory and ulcerative processes of stomach and intestines may show peritoneal involvement and lead to subsequent adhesions. Extensive adhesions in the pelvic peritoneum are extremely common as the result of gonorrhea in the female. Unless the causative inflammation be more or less continuous, as may be true of gonorrhea, the adhesion is simply a cicatrizing process and has a subsequent history similar to that of scars anywhere. The primary event is contraction of the scar so that viscera may be tightly bound together. In some instances the movement of the abdominal viscera may produce traction upon the scar and elongate it to form a fibrous band. As with congenital deformities of the peritoneum these adhesions of inflammatory origin may alter the position of viscera, and more especially where they are elongated to form bands or cords, may lead to strangulation of sections of intestine or produce obstruction by torsion.

Chronic peritonitis in order to be so classified must be a progressive chronic inflammation. Occasionally, a fairly widespread organizing fibrinous or chronic fibrous peritonitis may be observed, particularly as the result of chronic passive hyperemia and long standing ascites. Occasionally, a chronic peritonitis may in itself so dam back lymphatic outflow as to produce ascites. The involvement of peritoneum in the progressive fibrosing inflammations of serous membranes, called multiple serositis, is usually restricted to the subdiaphragmatic and upper part of the peritoneum. Chronic peritonitis may also appear in local forms upon the surfaces of organs, more particularly the spleen and the liver. There is a progressive deposit of fibrous connective tissue with thickening and stiffening of the capsule of the organ, and subsequent hyalinization to constitute the "zuckerguss" or sugary splenic or hepatic capsulitis.

Infectious Granulomata.—Tuberculosis of the peritoneum is most commonly the result of direct extension such as from tuberculous enteritis and mesenteric lymphadenitis. It may also extend from pleura, female internal genitalia, bones, adrenal and other viscera. Although it may occur as a part of a generalized miliary tuberculosis, it is not likely in this form to lead to such extensive lesions as when due to direct extension. Atrophic cirrhosis of the liver with its consequent disturbance of peritoneal circulation, apparently serves sometimes as a predisposing cause for peritoneal tuberculosis. In the acute form, miliary tubercles are found widely distributed over the surface of the peritoneum, in some cases associated with a mild acute fibrinous peritonitis, and even with an acute fibrinoserous peritonitis. In the more chronic forms the tubercles are larger and often fibrosed. Even in man, although the process is more characteristic in cattle, the tubercles may enlarge and show progressive fibrosis so as to constitute fairly large pearl-like masses, either sessile or pedunculated, constituting the so-called "perlsucht" disease. In the chronic forms of peritoneal tuberculosis, the fibrosis is not limited entirely to the tubercles and extensive adhesions are likely to be produced, sometimes to such an extent that it is difficult to separate one coil of gut from another. These ad-

hesions may be the result of an early acute fibrinous process or apparently may be entirely chronic in nature. Either with or without these adhesions, the chronic tuberculous peritonitis may be associated with an accumulation of a considerable amount of fluid. This varies in character from a fluid of low specific gravity with the characters of transudate, to that of higher specific gravity more nearly resembling serous exudate. It would appear that fluid accumulation may be due to faults in lymphatic drainage resulting from the tuberculosis, or may be due to the subacute or chronic inflammation with serous exudation. Hemorrhage into the fluid is not uncommon.

Tumors.—After a tumor of the peritoneum has developed it is often difficult to say whether it originated in the mesothelium, in the peritoneal con-

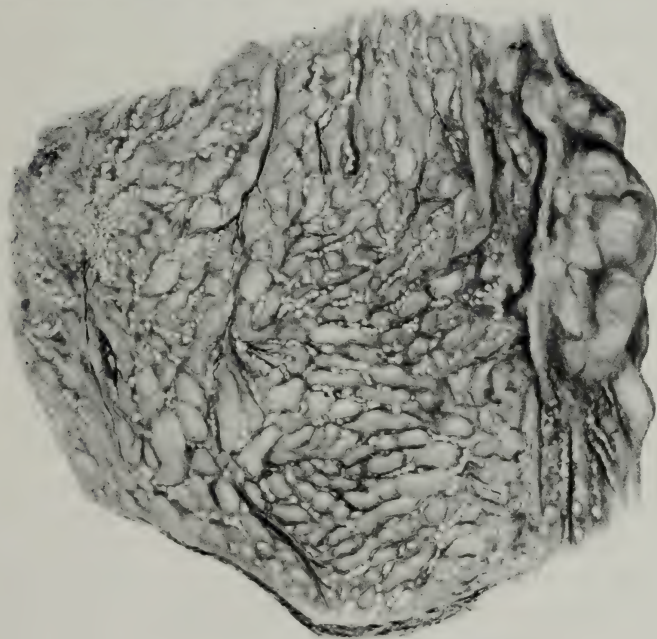


FIG. 289—Miliary tuberculosis of omentum.

nective tissue or in the underlying tissues. It is therefore advisable to discuss the tumors that affect the peritoneum without further reference to the exact site of origin. Benign tumors include lipoma, fibroma, myxoma, leiomyoma usually originating in the omentum, neurofibroma, ganglioneuroma, angioma both of lymphatic and blood vascular type, sometimes combined with endothelial proliferation to constitute angio-endothelioma. Various types of sarcoma are observed and there is also found a tumor called the endothelioma or mesothelioma, originating presumably from the mesothelium, growing as a more or less diffuse nodular mass and showing histologically sheets of cells of mesothelial or endothelial character. We have observed one such case in the omentum. It is always difficult, however, to distinguish between this type of tumor and an epithelial tumor which may have originated in misplaced epithelium. Cyst formation may occur in the lymphatics, more particularly

in the mesentery, and sometimes contain chylous material. Dermoid cysts, echinococcus cysts, and cysts formed by encapsulation of foreign material such as blood, are sometimes observed, and in intestinal pneumatosis the gas cysts may be observed in peritoneum and mesentery. Tumors of cystic character may show the same character in peritoneal metastases.

Secondary carcinoma of the peritoneum is common, originating particularly from carcinoma of the various organs partially or completely covered by peritoneum. Metastasis may also occur from more remote situations such as the breast. The nodules may be multiple and minute, somewhat resembling tuberculosis, or may be larger and more diffuse. The irritation of the tumor sometimes produces a low grade of inflammation leading subsequently to more or less extensive adhesions. According to extent or situation, ascites may appear or there may be a serous type of exudation. In either case, the fluid is likely to be somewhat bloody. An important source of secondary carcinoma of the peritoneum is the papilliferous cystadenoma of the ovary. Either infiltrating the omentum, mesentery, or extending diffusely over the surface of the peritoneum, the papilliferous structure is more or less reduplicated and there is poured out either into cysts or free into the abdominal cavity a large quantity of gelatinous mucous material. This constitutes one of the forms of pseudomyxoma peritonei (see Novak), but a closely similar condition grossly may be produced by secondary invasion of mucinous cancers from other points of origin. The rupture of cysts containing mucin or mucoid may determine the presence of considerable amounts of this substance within the peritoneum, usually leading to a variable degree of chronic fibrous peritonitis.

Foreign bodies include needles and similar metallic substances which may erode through the gut, and gall stones and other foreign bodies of the intestines entering the peritoneum because of perforation. Sometimes epiploic appendages become strangulated and detached and constitute foreign bodies. There are also found the so-called corpora libera, small firm pearly connective tissue masses, probably made up of organized cicatrized fibrin and resembling similar foreign bodies found in the joint cavities.

The encapsulation of small foreign particles, such as pieces of surgical sponges, small vegetable or other granules which may penetrate through ulcers or gain access to the deep lymphatics of the gut, may produce nodules, usually localized, which resemble tubercles grossly and show foreign body giant cells microscopically, the so-called foreign body tubercles or pseudotubercles.

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CHAPTER XVII

LIVER AND PANCREAS

LIVER

Congenital Anomalies.—The right or left lobes may be small or absent, and in severe general anomalies the liver may be absent. The lobes may show divergence from relative size and shape, may be more or less numerous than normal. If the left lobe be unusually large the organ is sometimes called the “beaver-tail” liver. A tongue-like downward projection of the right lobe, the so-called Riedel’s lobe may be confused with malposition of the kidney (Wilhelmi). The liver is on the left side in *situs viscerum inversus*. It may be much altered in position in diaphragmatic and umbilical hernias.

Acquired Abnormalities of Form and Position.—The contraction of scars, of wounds, ruptures, abscesses, etc., may produce deformities; and in syphilis the cicatricial contraction about gummata may produce a pseudolobation of the liver, the so-called *hepar lobatum*. The “corset” liver, due to pressure of corset, belt, etc., usually shows one or more folds in the upper surface of the liver, extending transversely (coronal) or obliquely, variable in depth, and in the depths of the fold sometimes showing fibrosis of the capsule. Pressure of a fixed costal margin in the aged, or in a kyphoscoliosis may produce much the same picture. Parallel sagittal folds in the upper surface, usually two or more in number, may be of congenital origin, or may be due to forced expiration, the result of disease of the lungs such as chronic emphysema. Abnormal folds of gut may leave their imprint upon the surface of the liver. As a result of cloudy swelling, passive hyperemia or other changes which produce a large soft liver, the impression of ribs may be seen on the upper surface.

Postmortem Change.—In addition to the general softening and autolysis which may affect the liver and which have been extensively studied (Wells), the most important postmortem change anatomically is the so-called foamy liver. This is due to the presence of anaërobic gas forming bacilli from the intestinal canal or from infected wounds. These multiply after death, especially if the body be kept warm, and produce numerous bubbles of gas. Decomposition proceeds rapidly and the liver becomes soft and spongy. Histological examination shows gas bubbles, dead cells, and numerous bacilli in the blood vessels.

Pigmentation.—In advanced life and also as the result of prolonged wasting diseases such as tuberculosis and carcinoma, the liver is sometimes the seat of brown atrophy. It is reduced in size and increased in consistency and shows externally and in the cut surface a deep brown color. The color is due to a relative and probably absolute increase in a non-iron bearing pigment normally present in the cells. Hemosiderosis in the liver is extremely common, particularly as the result of chronic passive hyperemia. The liver grossly may not show definite pigmentation, but microscopically the cells of the liver cords in the

central zone of the lobules contain quantities of iron bearing golden brown granular pigment. This may also be observed in small amounts in the endothelial cells of the sinusoids. In pernicious anemia and sometimes in profound secondary anemias the liver may be extensively pigmented with hemosiderin so as to be of light brown color to the naked eye. Microscopically, the iron bearing golden brown granules of pigment are found distributed in the parenchymatous cells throughout the lobules and not especially confined to the central zone.

Hemochromatosis probably affects the liver before the other organs. According to Mallory, Parker and Nye the pigment is in part hemosiderin and in part hemofuscin. They find that it is deposited first in the endothelial cells of the sinusoids and in the liver cells, then in the lining epithelium of the small bile ducts and in the connective tissue of the stroma. It may ultimately appear in the muscle cells of the blood vessels. It appears to be deposited first in the periphery of the lobules and later in the center. Grossly, the liver is deeply pigmented and usually the seat of a cirrhosis. It occurs in bronzed diabetes, as pointed out in the chapter on pigmentation, and there is a similar change in other organs, notably the pancreas. Ingestion of copper over long periods probably is the cause of many cases (Mallory).

In malaria the liver may be the seat of pigmentation visible to the naked eye. Upon microscopic examination pigment is found as dark brown granules, which do not respond to the iron test, situated principally in the endothelial cells lining the sinusoids. In argyria the silver pigment may be found under the endothelial cells of the sinusoids. Carbon is sometimes found in the form of opaque granules and spicules in the connective tissue due to transfer from anthracotic lung or mediastinal lymph nodes.

Bile pigmentation may be observed as a diffuse pigmentation of the liver in any variety of jaundice. The color of the fresh specimen is usually yellow but after oxidation of the bilirubin to biliverdin it becomes green. As the result of stasis of bile following obstruction either to the larger or smaller ducts, the pigment accumulates in small solid masses in the bile canaliculi within the cells and in the bile capillaries which course between the cells. This accumulation is more often observed in the center of the lobules than in the periphery but may be observed in either situation. The pigment masses may be phagocytosed by endothelial cells of the sinusoids and by migratory endothelial cells.

Degenerations and Infiltrations. Cloudy swelling is extremely common in the liver, particularly as the result of acute infectious diseases. Among other causes are passive hyperemia, general anemias, leukemias, poisoning by metals such as arsenic, antimony and lead, and other agents such as carbon monoxide alcohol, chloroform, iodoform and ether. The gross picture is usually altered by passive hyperemia, because the various causes of cloudy swelling of the liver affect other viscera and the circulatory apparatus. In a general way, however, the liver is somewhat enlarged, with a tense capsule. It is of reduced consistence, pallid in color, cuts with decreased resistance and shows a pallid, moist

bulging, friable cut surface. Microscopically, practically all the cells are affected, although as the result of passive hyperemia the lesion may be most marked in the central zone. The cells are swollen but their outline may be more distinct than usual, because the tension of the capsule leads to compression of the margins of the swollen cells. The cytoplasm is pale and distinctly granular. The nuclei are not affected. In passive hyperemia, where the lesion is most pronounced in the central zone, the dilated capillaries may prevent marked swelling of the cells. Hydropic degeneration or infiltration is probably simply an advanced stage of cloudy swelling, where the water imbibition is so marked as to lead to the presence of microscopically visible droplets. The center of the droplets of water may show a minute acidophilic mass which stains as does fibrin.

Fatty Degeneration.—Provided the cause be removed, cloudy swelling may progress to complete recovery, but with continuance or unusual severity of the same causes as those of cloudy swelling, the condition progresses to fatty degeneration. Prolonged passive hyperemia is especially likely to produce fatty degeneration in the central zones. The condition may also be observed around abscesses, infarcts, and areas of necrosis. In addition to the general conditions enumerated above, there are poisons that are particularly prone to produce fatty degeneration, notably phosphorus, phloridzin and certain fatty acids. As is true of cloudy swelling, the disease underlying the fatty degeneration also leads to passive hyperemia so that the condition is not often observed in uncomplicated form. Grossly, however, the liver is likely to be reduced in size with a flaccid capsule and sharp rather than rounded edges. The organ is soft, cuts with diminished resistance and shows a non-bulging or retracted cut surface. Both outer surface and cut surface are of yellow color. Microscopically, the lesion affects the central zone more strikingly than the peripheral zone. The cells may be enlarged but usually are reduced in size. The cytoplasm is granular, as a part of the cloudy swelling, and contains a variable number of minute fat droplets. The nucleus is usually normal but sometimes slightly pyknotic. The gross features may resemble more closely those of cloudy swelling when the fatty degeneration is of only slight degree, and the microscopic findings show only slight fatty degeneration. In most cases the two conditions are intermingled and one or the other may predominate.

Fat infiltration is the usual accompaniment of all the varieties of obesity. The accumulation of fat in the liver, therefore, is really an excessive demand upon the organ as a depot. In some forms this is due to overfeeding, and in others apparently the result of lack of oxidation of fat in metabolism. Fat infiltration appears also in connection with alcoholism, more particularly as the result of the ingestion of malted liquors rather than spirits, although this is not a fixed rule. It is supposed that in these instances the more ready oxidation of the alcohol for the production of energy protects the fats so that they accumulate. Fat infiltration of the liver is common in chronic tuberculosis, particularly of the lungs, quite regardless of whether the patient be obese or emaciated. It has been assumed that in certain of these cases this is due to

the excess fat in the dietary treatment of tuberculosis. On the other hand it is extraordinary that extremely emaciated individuals may show fat infiltration of the liver, and it is at least possible that there may be an alteration of metabolism, similar to that observed in cattle which sometimes fatten as the result of tuberculosis, operating in such a way as to lead to accumulation of, or protection of the fat of, the liver.

Amyloid.—The liver is one of the three organs, namely, the liver, spleen and kidney, which are readily affected by amyloid deposits. Chronic tuberculosis and chronic suppuration, syphilis and malignant tumors are the usual causes, although occasional cases are observed without definite cause. The organ is enlarged, firm, pale, shows rounded edges and a tense capsule. It cuts with normal resistance and shows a slightly bulging or non-bulging, pale, moist, slightly bleeding, more or less smooth glassy surface. Depending upon the degree of involvement the glassy character may be in numerous foci or diffusely distributed. The usual tests for amyloid, such as iodine and sulphuric acid, are diagnostic. Microscopically, the amyloid is found as a homogeneous hyaline mass, situated primarily between the endothelial cells of the sinusoids and the liver cords. This increases in size so as to compress and produce atrophy and complete disappearance of liver cords. As the disease progresses the larger masses may become more or less confluent, and amyloid is also observed in the arteries of the portal spaces.

Hyalin is observed grossly in cases of extensive thickening by fibrosis of the liver capsule, producing the so-called “zuckerguss” or sugary liver. Microscopically, it may be observed in the connective tissue masses in cirrhosis of the liver and in the blood vessels of the liver. Hyaline droplets may be found in the epithelial cells, more especially in cases of cirrhosis following alcoholism. *Glycogen* is normally present in the liver and may be increased by feeding with carbohydrates. It is commonly increased in diabetes mellitus.

Liver Necroses.—Aside from the necrosis incident to traumatic injury of the liver and its accompanying hemorrhage, as well as the necrosis that appears in infarction and abscesses, there is a group of necrosis which, in so far as human medicine is concerned, is caused principally by infectious disease and by passive hyperemia. As a rule, the liver, because of the infections or passive hyperemia, is the seat of cloudy swelling, fatty degeneration, passive hyperemia or all three. It is only rarely that the areas of necrosis affecting a part of the liver lobule are visible to the naked eye. Microscopically, the necrosis may affect the central zone, the middle zone or peripheral zone of the lobule and in some instances may be diffused through two or three of these zones. The necrosis may be granular in character or the cells may show hyaline transformation. In addition there is greater or less fragmentation of the liver cords. It is not uncommon in prolonged passive hyperemia to find that many of the cells of the central zone are the seat of necrosis, often associated with hemorrhage. Mallory believes that such *central necrosis* occurs only when in addition to the passive hyperemia there is infection of some sort. We have observed a few livers with passive hyperemia and central necrosis, but without infection,

general or otherwise. Lambert and Allison find that infection is no more common in such cases than in those without necrosis. Prolonged chloroform anesthesia produces a central necrosis, more likely to be hyaline than granular. This condition and its functional significance have been studied especially by Whipple and his colleagues. Acute yellow atrophy of the liver sometimes shows the necrosis predominant in the central zone. Various poisons, some of significance in industrial medicine, such as trinitrotoluene and carbon tetrachloride (Phelps et al.) and dinitrophenol (Warthin), may produce central necrosis. Experimentally, the injection of diphtheria toxin produces a central hyaline necrosis, but in human medicine there is more often a focal necrosis. *Midzonal necrosis* (of the middle zone) has been studied by Opie particularly, who finds that although it may appear in the middle zone around areas of hyperemia of the central zone, nevertheless, it may also appear as an independent process. In either instance it is associated with a variety of infectious disease. *Necrosis of the peripheral zone*, either focal or more extensive, is seen in eclampsia phosphorus poisoning, which may however be central, and experimentally following intravenous injection of chloroform (Schultz et al.). More diffuse necrosis involving two or more zones may result from extension of any of the conditions noted above, and also results from poisoning by mercury and arsenic. By *focal necrosis* is meant the death of a small group of cells, which may appear in any of the zones, but is probably more common in the middle zone than elsewhere. Focal necrosis is due to acute infectious diseases, outstanding among which is typhoid fever. Nevertheless, it may be observed in diphtheria, scarlatina, measles, septicemia and other types of infection. Experimentally, the injection of ether or of specific hemagglutinative and hemolytic immune sera also produces focal necrosis which is likely to be hyaline in character.

The degree of reaction to the necrosis depends in part upon the extent of the lesion and the length of time the patient or animal survives the injury. Infiltrations of polymorphonuclear and mononuclear cells, particularly the endothelial type of cell, is variable. In some instances the polymorphonuclear leucocytes predominate, especially in the earlier stages. In others, notably the focal necrosis of infectious disease, although the polymorphonuclear leucocytes predominate early in the lesion, in the later stages the infiltration is principally by mononuclear endothelial cells. The infiltrating cells are actively phagocytic and aid in the removal of the detritus. According to Mallory, fixed tissue reaction occurs only when the necrosis has affected the connective tissue. Thus, the more extensive and severe forms of necrosis may ultimately lead to extensive scar tissue formation with multiplication of bile ducts in an attempt at regeneration. Thus, a picture of a cirrhosis of the liver may be observed.

Numerous observers, including Flexner, Opie, Warthin, and others, have noted the presence of thrombi in the capillaries. The studies of Mallory and of Opie indicate that occlusion of the sinusoids by small foreign bodies may produce necrosis. This, however, is not so extensive as is observed in other conditions. Our own studies show that the circulation in the sinusoids is not entire-

ly obliterated by the presence of the hyaline thrombi of immune serum necrosis. Mallory has indicated further that occlusion of the sinusoids by endothelial cells transferred from the spleen is associated with the focal necrosis seen in typhoid fever. It seems probable, however, as the result of our investigations and of those of others, that in addition to the partial or complete occlusion of the circulation of the sinusoids, there must be in addition some cytolytic or cytotoxic action. Functionally, there may or may not be severe disturbance attributable to the liver. In the more extensive necrosis, jaundice is not uncommon (Oertel), but it is at least probable that the jaundice is not only obstructive due to interruption of the bile canaliculi but also of hemolytic origin due to the same cause which leads to necrosis. Whipple finds that the amount of fibrinogen in the blood is reduced, probably accounting for decreased coagulability of the blood, and that the amount of lipase is increased. The ammo-

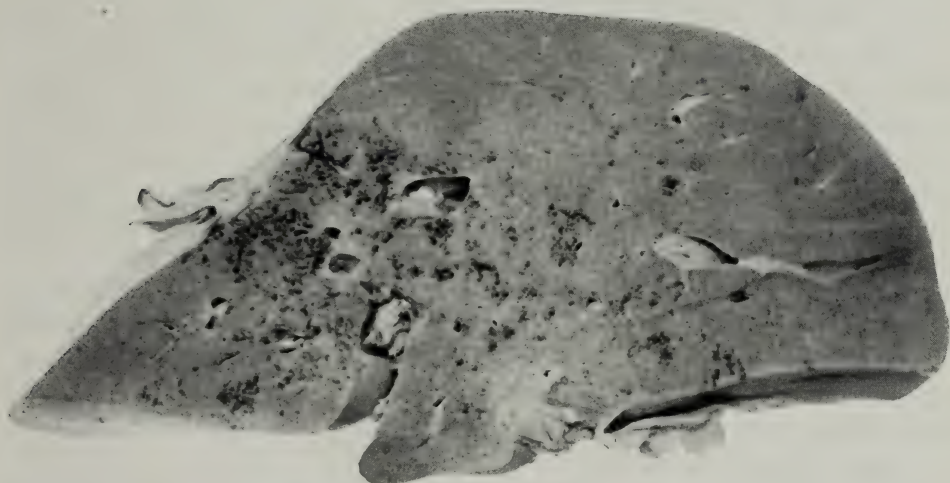


FIG. 290—Hemorrhagic necrosis in liver of eclampsia.

nia of the urine may be increased in certain conditions of this kind, indicating a reduced protective action on the part of the liver, although as the result of perfusion studies by Fiske and Karsner it could not be demonstrated to be due to the liver alone. Marshall and Rowntree, and Simonds and others have studied the functional alterations in experimental liver necroses. There is found in addition to the alterations in fibrinogen and lipase an accumulation of non-protein nitrogen in the blood, a reduced tolerance to sugars and usually a terminal acidosis.

Eclampsia.—This is one of the toxic complications of pregnancy and usually appears in the later months or in the early puerperium, but is occasionally observed early in pregnancy. Clinically, in addition to decreased urinary output and subcutaneous edema, the outstanding features are convulsions, often associated with persistent vomiting. The anatomical lesions are most striking in the liver but these do not correspond in severity with the clinical manifestations. There may be merely hyperemia, fatty degeneration, small foci of

necrosis and slight leucocyte infiltration or there may be massive infarcts, necroses and hemorrhages. More characteristic is extensive fatty degeneration, hyperemia, hemorrhage and small areas of necrosis. Microscopically, the areas of necrosis are small or extensive and are in the periphery of the lobule. The cell cords are disorganized, the cells are the seat of cloudy swelling and necrosis and often contain vacuoles (not fat) in the cytoplasm. The sinusoids often contain hyaline thrombi and sometimes syncytial masses, apparently from the chorionic villi. The process may merge into an acute yellow atrophy. The kidneys usually show severe degeneration, with foci of necrosis of the tubular epithelium but in rare cases escape damage. The heart may also show myocardial degeneration. The central nervous system may show areas of hemorrhage, necrosis and vascular thrombosis.

The cause remains obscure, but many investigations point to an intoxication originating in the placenta. As pointed out by Wells, the ductless glands are not responsible. McQuarrie's suggestion that it is due to admixture of incompatible blood from the fetus is not established. Infection cannot be shown to play a part. Although excision of the breast of cattle seems beneficial it is not effective in women. Paramore does not provide adequate support for the assumption that the intoxication is secondary to the visceral lesions. Goldzieher in his admirable review of the subject regards vascular occlusion by thrombi and placental emboli as of great importance, but they probably are not primarily significant because emptying the uterus is often followed by complete recovery. The latter fact implicates placenta or fetus. The fetus is usually normal in every respect although it may show the same lesions as the mother. Leipmann and Schulz find that the placenta gives off increased amounts of nitrogenous products and consider this organ to be the source of the poisons. The problem, however, is still unsettled. The disturbances of metabolism seem principally to affect proteins (Williams).

Acute Yellow Atrophy.—This misnomer is applied by common usage to a condition in the liver essentially necrotic in character, associated with marked reduction in size; in the earlier stages the organ is yellow and in later stages red. It is most common in early adult life and attacks females much more often than males. It runs a course varying from a few days to a few weeks, usually initiated with gastro-intestinal symptoms followed by reduction in size of liver, jaundice, coma, and sometimes multiple hemorrhages in various organs. It has not been demonstrated to be of bacterial origin but has been observed in cases of smallpox, erysipelas, peritonitis, septicemias, and in the secondary stage of syphilis. The character of the lesion of the liver, as well as the preceding gastro-intestinal disturbance, suggests that poisons generated in the gastro-intestinal canal may be of importance. It occurs in pregnancy either as a primary acute yellow atrophy or as secondary to eclampsia. It may apparently arise in otherwise perfectly good health. The possible causes and the functional disturbances are admirably reviewed by Wells. The urine characteristically contains leucine and tyrosine as well as other amino-acids and purines. Analysis of the liver shows the presence of essentially the same

products. The blood is much the same as in many other liver necroses except for the large amount of leucine, tyrosine, other amino-acids and bile pigments and salts. Whereas in chloroform, phosphorus and amanita phalloides poisoning, the early change affects the cytoplasm principally in the form of fatty degeneration with necrosis as apparently secondary, in acute yellow atrophy the necrosis is primary, the nuclei being destroyed early in the course of the condition and the cytoplasm undergoing autolysis subsequently. The relation of these processes is admirably discussed by Herxheimer. At autopsy the liver is found to be much reduced in size, sometimes as small as 750 grams, and is situated well toward the spinal column. The organ is extremely soft, somewhat elastic, shows sharp edges and a wrinkled capsule. Through the capsule numerous yellow or grayish-red, often slightly depressed, patches are observed. The organ cuts easily and the cut surface usually retracts. It is soft, distinctly friable and of diffuse yellow color. In somewhat later stages however, the yellow may be mottled with red and in still later stages the color may be a diffuse yellowish-red. In the red areas the consistence is less "mushy" than elsewhere. Upon exposure to the air the color may become green, since it is largely due to bile pigment. In later stages, when connective tissue growth has partly replaced the necrotic liver substance and regeneration is in progress, the consistence is greater than in the early stage and ultimately there may be a condition simulating cirrhosis. Microscopically, the degenerative and necrotic processes are almost coextensive with the lobules, and in our experience the most severe lesion has been in the central part of the lobule. In the necrotic areas the nuclei are completely absent and the cytoplasm may be granular, the seat of fatty degeneration, or has completely disappeared. In areas of complete disorganization, albuminous granules, small globules of fat, small solid masses of bile pigment and crystals which are probably crystallized bile pigment are found. The sinusoids are often widely distended and in the disorganized area small foci of hemorrhage are observed. When the liver is red these areas of hyperemia and of hemorrhage are more pronounced. If the patient survive, fibrosis and regeneration make their appearance. The connective tissue grows principally from the preëxisting connective tissue of the portal space and with it there is extensive multiplication of bile ducts. In a case which we observed that had lived five weeks from the onset of the attack, fibrosis and bile duct proliferation were pronounced but the lobular substance was still the seat of marked necrosis. As in cirrhosis of the liver, the bile duct proliferation may result in the formation of pseudolobules resembling in a certain measure regenerated lobular tissue.

Circulatory Disturbances. Passive Hyperemia.—Passive hyperemia of the liver is due principally to chronic disease of the heart or failure of the myocardium in decompensation. It may also be the result of chronic diseases of the lung with stasis in the right side of the heart, to tumors or fluid in the thorax compressing the inferior vena cava, or to disease within the inferior vena cava itself. The distance between the entry of the hepatic vein into the inferior vena cava and of the latter into the right atrium is so short, that effects

are felt very quickly in the central veins and the sinusoids. The appearance of the liver varies considerably, depending upon the duration and degree of the hyperemia. In the earlier stage the liver is large, with tense capsule, rounded edges, fairly firm and of dark red or purple color. It cuts with normal resistance and shows a soft, bulging, freely bleeding cut surface in which the central zones are found to be dark red or purple, enlarged and somewhat depressed below the slightly bulging, yellow or brown peripheral zone. In a later stage the liver may be normal or reduced in size and the color altered by the presence of cloudy swelling or fatty degeneration. Because the liver loses much blood by draining into other tissues after death, the organ may be much larger in life



FIG. 291—Passive hyperemia of liver, showing enlarged central zones.
Army Medical Museum 13354.

than at autopsy. Owing to the peculiar lobular construction of the human liver, the distension of the central zones may become so great as to establish what appears grossly to be an interlacing network of communicating, red, slightly depressed central zones. At this stage there is usually well marked fatty degeneration of the surrounding liver cells. This constitutes the so-called nutmeg liver of chronic passive hyperemia. Still later the liver is considerably reduced in size and is said to be the seat of red atrophy. This may represent either an advance of the nutmeg liver or may not have been preceded by any such condition. The liver in later stages, when the lesion is definitely chronic, may be relatively increased in consistency, and under these circumstances may be referred to as the seat of cardiac or central cirrhosis. Microscopically, it is possible, as pointed out by Lambert and Allison, to distinguish several grades or degrees of change in passive hyperemia. The simplest is that in which the

central vein and the immediately neighboring sinusoids are widely distended with blood. In association with this the central cells show reduction in size. Although most observers regard this as an atrophy of the cells, Mallory states that in many cases it is an elongation rather than an atrophy. There is likely to be hemosiderosis of the central cells and cloudy swelling of all the cells. Edema, especially evident between the sinusoidal endothelium and the liver cords, may be present. In another type of lesion there may be fatty or vacuolar degeneration of the central cells without true necrosis, and although this is the result of passive hyperemia the latter condition may not be clearly demonstrable. In some instances the cells of the central zone may be so swollen by cloudy swelling and advanced fatty degeneration that the sinusoids in that region are not dilated, but in the immediately neighboring middle zone there may be marked hyperemia. Central necrosis has been referred to above. In the so-called cardiac or central cirrhosis, modern observation indicates that the firmness is due to a relative increase in connective tissue following the atrophy and necrosis of parenchymatous cells. There is probably no increase in the actual amount of connective tissue and there is no reason for believing that a nodular variety of cirrhosis can be caused by passive hyperemia. Functionally, as far as can be demonstrated by the available tests, there is little disturbance as the result of even the most pronounced passive hyperemia, except in those cases where necrosis has supervened.

Embolism.—As with embolism of other organs, the primary cause may be found in the arterial system with transport to the liver through the hepatic artery, or in the tributaries of the portal system with transport through the portal vein. Thus, endocarditis, arteritis, thrombophlebitis, sclerosis, thrombosis and other similar lesions may produce embolism in the liver. Rarely, retrograde embolism from the inferior vena cava or the right heart may occur into the hepatic vein.

Thrombosis.—Thrombosis in the portal vein may be due to tumors either primary or secondary within the liver, compression by tumors, gall stones, and other lesions outside the liver, cirrhosis of the liver, thrombophlebitis, cholangitis. As pointed out by Webster, thrombosis of the portal vein under any of these circumstances is unusual without associated sclerosis of the vein. Occasional cases occur without lesions other than this sclerosis. Thrombophlebitis in any part of the portal tributaries may progress so as to involve the chief vein. The same conditions may cause thrombosis in the hepatic veins. Thrombosis of the hepatic artery is usually due to arteriosclerosis but may be

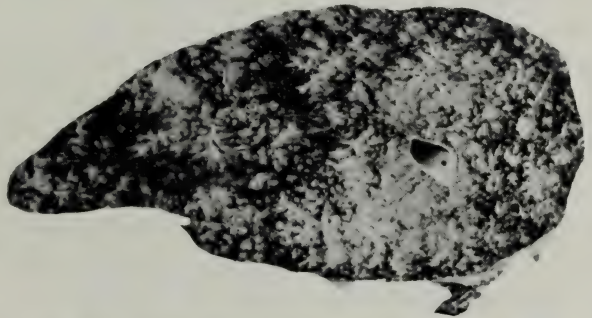


FIG. 292—Chronic passive hyperemia of the liver with fatty degeneration ("nutmeg" liver).

of embolic origin. Occasional cases of aneurysm of the hepatic artery are observed and these may be complicated by thrombosis.

The extensive anastomosis within the liver of branches of the hepatic artery and of the portal vein, both within their own circulation and between each other, is such that the occlusion of the intrahepatic branches, as pointed out by Winternitz, often has no observable effect. Occlusion of the main branch of the portal vein may lead to no change in the liver other than a moderate hyperemia. There may, however, be some atrophy of the liver cells. Similarly, occlusion of the hepatic vein may produce a distinct hyperemia or no effect. Either of these conditions may produce passive hyperemia of the vessels of the abdominal cavity, with hyperemia of the intestines, enlargement of the spleen and sometimes ascites. The establishment of collateral circulation through the hepatoduodenal ligament may relieve the passive hyperemia in the abdomen. Occlusion of the main hepatic artery may lead to death. If the lesion affect its smaller branches, there may be no change or there may be infarction. The nutrition of the cells under various circulatory conditions has been studied by Bainbridge and Leathes.

Infarction.—This lesion in the liver is distinctly unusual. Pale yellow areas near the surface, somewhat resembling infarction, are frequently observed, but there is no necrosis. The so-called atrophic red infarct of Zahn cannot be regarded as a true infarct since there is only hyperemia and atrophy of the parenchymatous cells. As observed at autopsy most infarcts of the liver are hemorrhagic although some may be white or anemic. They may be of conical or of cylindrical form, usually sharply defined, and either swollen or retracted, depending upon duration. Collateral hyperemia is not marked and reactionary fibrosis is usually slight in degree. Rolleston maintains that the most frequent cause is occlusion of the intrahepatic branches of the portal vein, which may be due to any of the causes enumerated above. Occlusion of the hepatic arteries may produce infarcts although, as indicated by Baldwin, it seems likely that some general passive hyperemia of the liver is probably necessary in order for such occlusion to lead to actual necrosis. There is little doubt that coincident occlusion of both hepatic artery and portal vein may produce infarcts. Traumatism leading to rupture of the liver or to direct injury of the liver as by bullet wounds may, by extensive occlusion of vessels, lead to infarction. It must be admitted, however, that as yet modern experimental procedures have not been extensively directed toward solution of the problem of this unusual occurrence in the liver.

Hemorrhage in the liver occurs as the result of vascular occlusion, chronic passive hyperemia, especially with necrosis, eclampsia, phosphorus poisoning, various infectious diseases, hemorrhagic diseases, infarction, traumatism, and may be observed as subcapsular hematomas in infants born of mothers suffering from infectious or toxic diseases.

Acute Suppurative Inflammation.—The infectious agent producing suppurative inflammation of the liver, or abscess formation, may be introduced through the portal vein, the hepatic artery, the hepatic vein, the biliary

passages or by direct extension. With few exceptions, such as amebic abscess and those forms which occur as the result of direct extension, this lesion in the liver is usually multiple. The most common mode of entry is through the portal vein as the result of ulcerative or suppurative lesions connecting with its tributaries. Suppurative or ulcerative appendicitis with peri-appendiceal abscess constitutes the most common point of origin. Ulcers and suppurative lesions of the stomach, small and large intestines are of importance. Among these is bacillary dysentery, which has been discussed in the preceding chapter. Abscesses in such organs as pancreas, spleen and especially abdominal lymph nodes may cause abscess in the liver. Nevertheless, multiple abscess of the liver is occasionally found without any demonstrable portal of entry. In this group of cases, however, it is important always to examine for actinomycetes

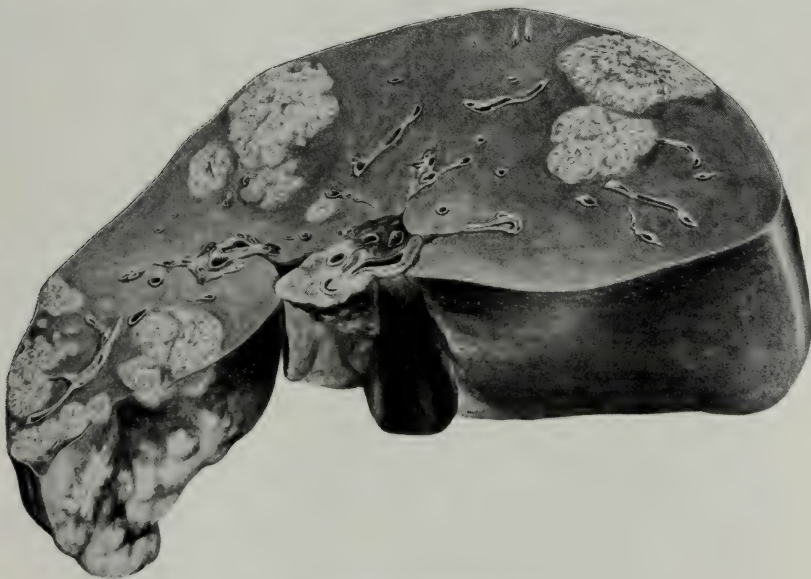


FIG. 293—Multiple abscesses of liver.

which may gain access to the liver without gross lesion of the intestine. The infection in the liver starts, as a rule, as a suppurative thrombophlebitis of the smaller tributaries of the portal veins. From this lesion emboli are detached and lodge in the intrahepatic branches of the portal vein. Occasionally, the extension is by a progressive thrombophlebitis extending along tributaries to the main stem of the portal. Grossly, the liver is usually somewhat enlarged, dark and either gray or yellow, depending upon the degree of associated cloudy swelling or fatty degeneration, or green in color due to the escape of bile. The capsule is tense and smooth, except when abscesses near the surface involve the capsule in an acute fibrinous or fibrinopurulent perihepatitis. Upon cross section the abscesses are found distributed more or less uniformly throughout the liver, but as a rule are much more numerous in the right than in the left lobe. They may vary in size from 3 mm. to several centimeters. The outline is often irregular, giving the impression that several small abscesses have

coalesced. The degree of destruction of liver tissue varies. Trabeculae of connective tissue may course through the abscess and sometimes fairly solid masses of necrotic liver cells are observed. The pus may be yellow, green, non-odorous, or very foul, depending upon the type of organism involved. The origin is such that colon bacilli frequently contaminate the abscess area and

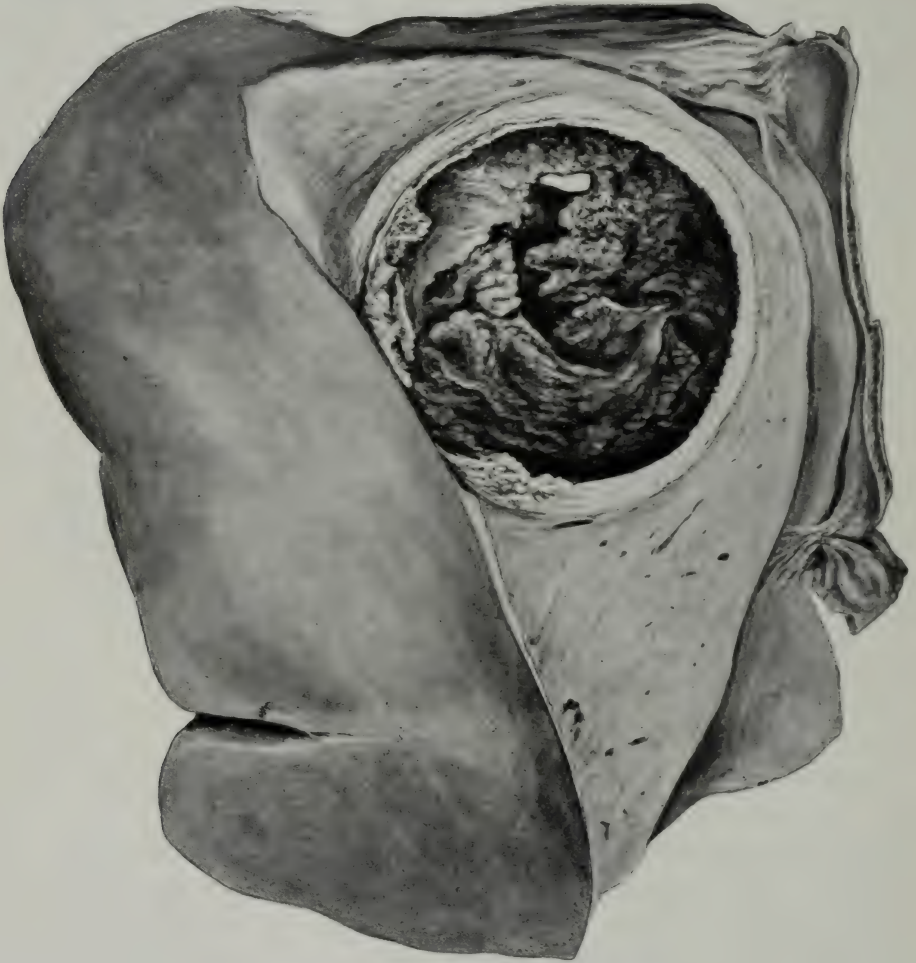


FIG. 294—Solitary tropical, or amebic abscess of liver.

other gas formers may gain entrance. There is usually a marginal zone of hyperemia. The liver shows variable degrees of hyperemia, cloudy swelling, fatty degeneration and sometimes bile stagnation. Microscopically, it appears that the organisms in the emboli multiply rapidly so as to fill a branch of the vein, around which there is a zone of leucocytes, further surrounded by a zone of necrotic liver cells. This primarily portal situation of the abscess may rarely be noted grossly. As the area of suppuration increases in size it is often preceded by the necrosis of liver cells and a small zone of hyperemia. Fatty

degeneration is often more pronounced in the neighborhood of the abscess than elsewhere in the liver.

Tropical abscess due to the *endameba histolytica* has been extensively studied by Councilman and Lafleur and by Howard and Hoover. This differs from most other abscesses in that it tends to be solitary and to run a protracted course. Whereas most other abscesses are fatal, this is by no means necessarily so. The infectious agent in all probability enters through the portal vein and after lodgment exercises its necrotizing powers upon the liver substance. Around the area of necrosis there is an infiltration of cells, principally mononuclear endothelial cells and lymphoid cells with relatively few polymorphonuclear leucocytes. In spite of the development of a connective

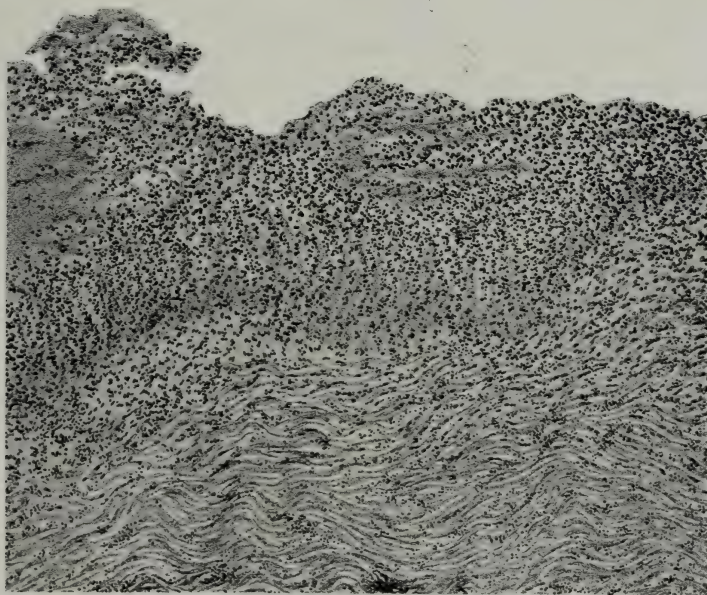


FIG. 295.—Marked fibrosis in wall of amebic abscess of liver.

tissue reaction in the margin, the abscess slowly extends and may reach very large proportions. Rupture may lead to a generalized peritonitis and death, although surgical puncture of the abscess by a trocar is frequently practiced without danger, because of the presence of protective fibrous adhesions. Although the abscess content may be purulent it is more commonly soft, granular and cheesy. Occasionally, jaundice may accompany the lesion. It is only rarely that tropical abscess is multiple. The solitary abscess is usually in the right lobe, may grow to enormous size and as much as eight liters of purulent material have been removed.

The hepatic artery and the hepatic vein only occasionally furnish a portal of entry for liver abscess. In cases of endocarditis or of pyemia, emboli may enter through the hepatic artery. When abscesses occur in this way they are usually multiple but small, and often appear to follow the distribution of one of the smaller branches of the artery. A suppurative thrombophlebitis of the

inferior or superior vena cava may extend by retrograde thrombosis or embolism into the liver. Such an occurrence is rare.

Suppuration in the gall bladder and biliary passages may extend along the intrahepatic biliary passages and produce multiple abscesses of the liver. Generalized jaundice is common in this condition and the contents of the abscess are usually bile stained. Although at autopsy the exact origin of such abscesses may not be apparent, yet the presence of jaundice and more particularly the presence of a more or less generalized suppurative cholangitis indicates the derivation.

Abscesses in the liver arising by direct extension are usually superficial. Such a process may extend from suppurative disease of the gall bladder or bile passages, subdiaphragmatic abscesses, abscesses of kidney and perirenal tissue, pancreas and other neighboring positions, and may result from perforation of ulcers of stomach and duodenum. Sharp foreign bodies may penetrate through stomach or intestine and lodge in the liver to produce abscess formation.

Acute Non-suppurative Inflammations.—Although these conditions are not common at autopsy, there appear to be many clinical cases which can only be explained on the supposition that such a lesion is present. Acute parenchymatous hepatitis occurs under the same conditions as does cloudy swelling, namely, as a part of the acute infectious and toxic diseases. Grossly, the liver is not distinguishable from that of cloudy swelling, but microscopically in addition to the cloudy swelling there is found a moderate infiltration of polymorphonuclear leucocytes in the perilobular connective tissue, sometimes with slight extension down between the cords of liver cells. Acute interstitial hepatitis of non-suppurative variety may occur under the same circumstances, but according to Adami is more frequent in typhoid fever and tuberculosis. It shows nothing more than cloudy swelling grossly, but microscopically differs from the parenchymatous form in that instead of there being an infiltration of polymorphonuclear leucocytes, there may be in the same distribution mononuclear endothelial and lymphoid cells. It is probable that both these conditions may heal without any sequel, but it is at least possible that they may constitute an original lesion for the later development of cirrhosis.

Chronic Interstitial Hepatitis. Cirrhosis.—As with other parenchymatous viscera, it is often difficult to distinguish in the liver between fibrous overgrowth representing cicatrization and that which is progressive in character and regarded as chronic inflammation. In certain cases it is easily possible to recognize scar formation. In most instances, however, it is plainly evident clinically that the more diffuse forms of connective tissue overgrowth are progressive in character, histologically show lymphoid and other mononuclear cells in the masses of connective tissue, and therefore are regarded as chronic inflammations. This progressive overgrowth of connective tissue, with the associated changes in the parenchyma, is usually referred to as cirrhosis of the liver. The most common variety of cirrhosis of the liver is that called atrophic cirrhosis. Other forms include obstructive biliary cirrhosis, capsular cirrhosis,

syphilitic cirrhosis, the so-called central cirrhosis following passive hyperemia, and hypertrophic biliary cirrhosis. These conditions are variously classified by writers on the subject and are covered in the publications of Rolleston, Castaigne, Epplen and others. It is not clearly apparent, however, that in these various diseases there is sufficient uniformity of cause or effect to justify classification of them all as a part of one great unit. Our consideration will attempt to group them in so far as possible. That form due to syphilis will be considered with the subject of syphilis rather than under the cirrhosis. The

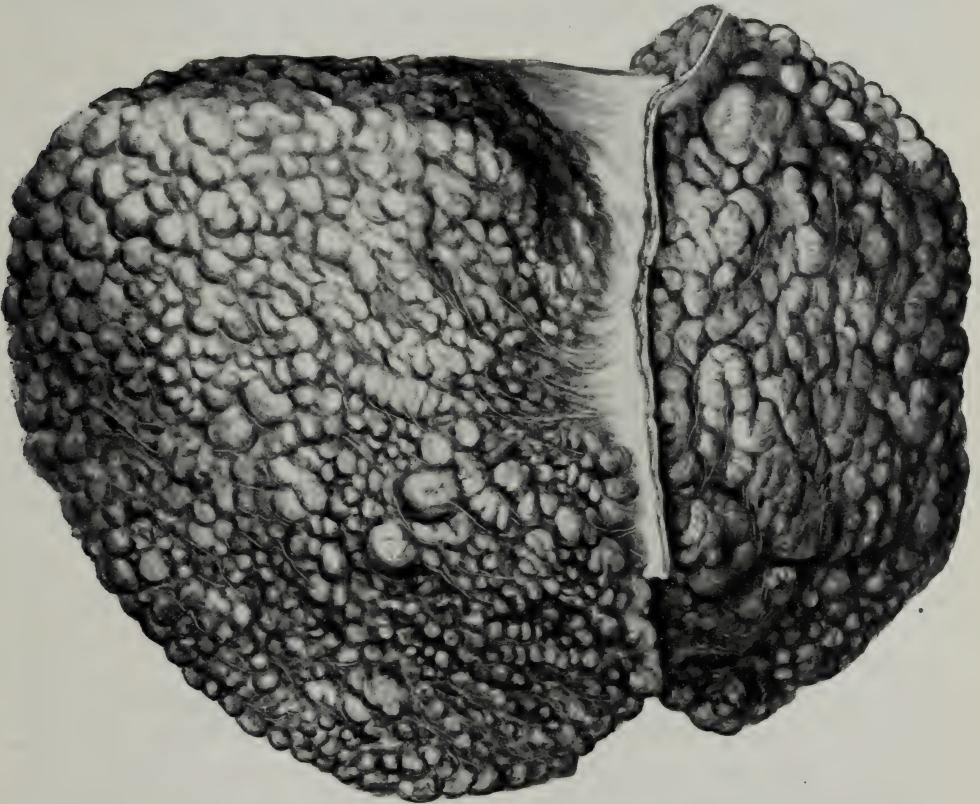


FIG. 296—Outer surface of atrophic cirrhosis of the liver.

term cirrhosis, indicating a yellow color, is a misnomer, since many of the livers are not of yellow color.

Atrophic Cirrhosis.—This is also called the cirrhosis of Laennec, portal cirrhosis, the gin drinker's liver, hob-nail liver, and granular cirrhosis of the liver. Clinically, it is the variety of cirrhosis associated with ascites, and exhibits jaundice in about one third of the cases for short periods or as a terminal event. It is a disease of the male sex and middle life, sometimes appears to be familial, and since it commonly appears in drinkers of spirituous liquors, may have an occupational significance. Although alcohol plays an important part as an apparent cause clinically, it has not been possible to produce the lesion experimentally in animals by the use of alcohol. Certain studies seem to

controvert this statement, but most of the work has been carried out with rabbits, which often show a similar lesion non-experimentally. It is possible that in man the digestive disturbance incident to chronic alcoholism may cause the disease rather than the alcohol itself. Clinically and pathologically a few cases seem to indicate that the deposit of foreign material, such as carbon and silica, may produce a cirrhosis. Mallory's studies as well as certain clinical observations indicate that copper will induce a cirrhosis. In Mallory's opinion, upon an experimental basis, it would appear that a deposit of hemosiderin and hemofuscin leads to the overgrowth of connective tissue. Clinically, it would appear that arsenic and lead would produce the disease. Although chloroform poisoning does not ordinarily lead to cirrhosis, Opie has found experimentally, that the use of chloroform associated with the injection of colon bacilli produces a condition closely similar to human cirrhosis. In all probability acute and chronic infectious diseases will rank with alcohol in the field of etiology. During the course of infectious disease there is not only degeneration of the parenchymatous cells but in many instances necrosis. There is no doubt that occasional cases of cirrhosis can be traced to infectious disease and it is possible that others may be due to the same cause. As a sequence of necrosis extensive fibrosis may occur and this can be progressive. In the more chronic infections it is possible that the poisonous products may coincidentally produce deterioration of the parenchyma and stimulation of connective tissue growth. Although Opie's experimental work, quoted above, would indicate that bacteria are of importance, there is no concrete evidence in human medicine for stating that cirrhosis is due to the direct effects of bacteria. In addition to the quotations above, experimental cirrhosis has been produced by Gye and Purdy using colloidal silica, Jaffe using amyl alcohol and phenylhydrazine, Pearce using hemolytic immune sera, Wells using Witte peptone, Findlay using magnesium chloride and Davidson using coal tar.

Various workers have suggested that the parenchymatous change is primary and that the fibrosis is only for substitution, whereas others believe the fibrosis is primary and compresses and destroys parenchyma. If it be conceded, as to us seems probable, that the condition is essentially inflammatory, the most suitable explanation is that the two lesions go hand in hand (Hall and Ophüls).

In the early stages of the disease clinically, and sometimes at autopsy, the liver is slightly enlarged. In the vast majority of instances it is very considerably reduced in size and weight, although owing to the relative predominance of connective tissue the specific gravity is increased. The shape is usually about normal since the process involves fairly equally the entire liver. The edges are usually sharp, although in those cases where there is associated fat infiltration they may be rounded. The color is ordinarily a reddish-brown but may be yellow due to fat infiltration or yellowish-green due to bile stagnation. The outer surface is uniformly nodular, sometimes more strikingly so in the lower surface. In different cases nodules may be small varying between 2 and 3 mm. in diameter, or larger, ranging in the neighborhood of 5 mm. in diameter. They are generally spherical, well-defined, project above the outer surface,

are relatively soft, and are of reddish-brown or brownish-yellow color, separated from one another by dense gray, retracted, connective tissue network. The organ is firm in consistence and cuts with leathery resistance. The cut surface is firm, more or less retracted, and shows an interlacing network of dense gray fibrous connective tissue, with intervening, slightly bulging parenchymatous tissue similar to that seen in the nodules on the outer surface. The connective tissue is distributed in a general way in accordance with the arrangement of perilobular connective tissue, and the size of the nodules depends in part upon the number of lobules included in the connective tissue network. In cases

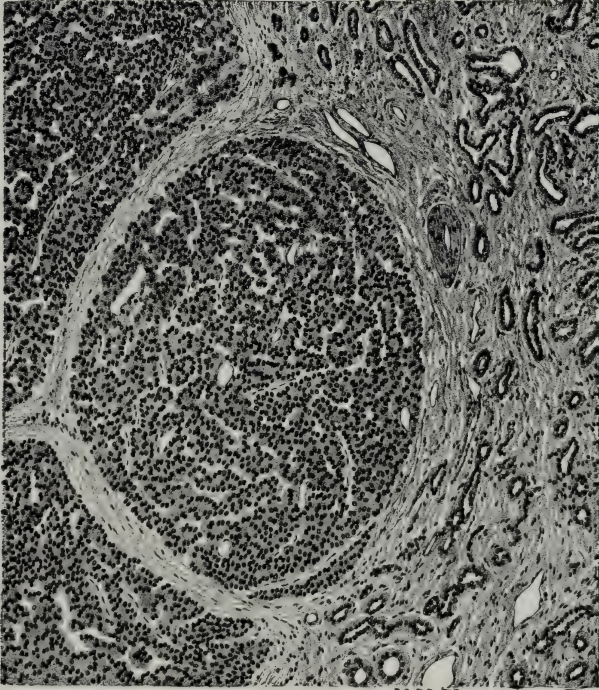


FIG. 297—Atrophic cirrhosis of liver showing multiplication of interlobular bile ducts.

where the nodules are small the condition is referred to as a monolobular cirrhosis; where larger it is referred to as multilobular cirrhosis. This distinction is not strictly accurate since in the smaller nodules several lobules are likely to be included. Often there are found not only on the outer surface but also in the cut surface, nodules of light yellow color and of soft consistence which represent areas of so-called nodular regeneration. These represent an attempt to reproduce liver lobules, never fully successful as to architecture. When the cirrhosis is a part of hemochromatosis, the brown color of the liver is obvious and the organ responds even grossly to the potassium ferrocyanide-hydrochloric acid test for iron.

Histologically, if the section be taken near the surface, the irregular surface outline is observed. The capsule is normal or only slightly thickened over the

nodules but usually dense and fibrosed in the interspaces. Instead of the normal arrangement of perilobular connective tissue, only partly dividing lobules from one another, there is a complete lobulation by the thick fibrosis. Within the oval or circular spaces of this network one or more lobules may be identified. As a rule, the connective tissue is of adult type, rich in fibrils and with dense nuclei, but occasionally, younger types of fibroblastic connective tissue cells are observed. There is a variable infiltration of lymphoid cells sometimes associated with endothelial and plasma cells and even a few leucocytes. Within the dense masses of connective tissue there is found a definite increase in the number of small bile ducts. These appear to ramify through the connective tissue and often show clubbed ends suggesting an attempt at new formation of lobules. Indeed, the extension of the bile duct with the clubbing of the ends may go on to the formation of large masses of irregularly distributed and arranged cells, morphologically similar to those of the liver cords. These do not show definite cord-like arrangement, show little in the way of bile canaliculi and are not regularly vascularized. In the gross they may constitute large, pale, soft nodules. It is assumed that with the destruction of functional liver substance there is a reversion to the embryonal type of development of liver so that the bile ducts make the attempt to contribute new liver substance. There is no doubt, however, that liver cells can play a large part in regeneration and this may be responsible for scattered small groups of a few liver cells isolated in the dense connective tissue. As a rule the connective tissue overgrowth is sharply defined, but occasionally branching processes of connective tissue penetrate a short distance between the cords of the lobules. The parenchymatous cells are definitely reduced in number and are usually the seat of variable degrees of cloudy swelling, sometimes with slight fatty degeneration in the central zones. As a rule, the central cells are small and appear to be atrophic but the peripheral cells may be larger than normal and are presumably hypertrophic. The nuclei vary in size and in staining capacity and sometimes show budding forms within the cells suggesting amitotic division. Not infrequently moderate hemosiderosis of the central zone is observed. In the cases with prolonged jaundice, bile pigment may be found in the canaliculi and bile capillaries.

Not uncommonly, a considerable amount of fat infiltration, showing the usual characters grossly and histologically, accompanies an atrophic cirrhosis. In these instances the liver may not be materially reduced in size. The condition is often referred to as fatty cirrhosis, but there is no particular reason for believing that the fat infiltration is other than an ordinary infiltration superimposed upon the cirrhosis or accompanying the cirrhosis, nor is there any positive reason for stating that the cause of the two conditions is the same. Atrophic cirrhosis is not distinguishable anatomically or functionally from that described above accompanying Banti's disease. A similar process in the liver, usually multilobular in type, frequently accompanies progressive lenticular degeneration, the so-called Wilson's disease. In hemochromatosis the anatomy of the liver is essentially the same as that in atrophic cirrhosis except for the presence of the pigment.



PLATE XVIII—Atrophic cirrhosis of liver stained by the Mallory special stain for connective tissue.

Atrophic cirrhosis may progress far anatomically before functional changes are demonstrable. In the later stages there may be a failure of the liver to destroy the ammonia absorbed in the intestines, although Hewlett thinks that excess of ammonia in the urine is due rather to acidosis; the amino-acid content of the urine may be increased, there may be a reduction in the formation of fibrinogen with reduced clotting capacity of the blood (Whipple), the fibrinolytic activity of the circulating blood is increased (Goodpasture), urobilin may appear in the urine, jaundice may supervene (see Opie, Carlson, Mann, Greene). The outstanding functional disturbance is in the portal circulation. Passive hyperemia in the portal vein and tributaries produces the usual secondary changes of passive hyperemia in the abdominal viscera such

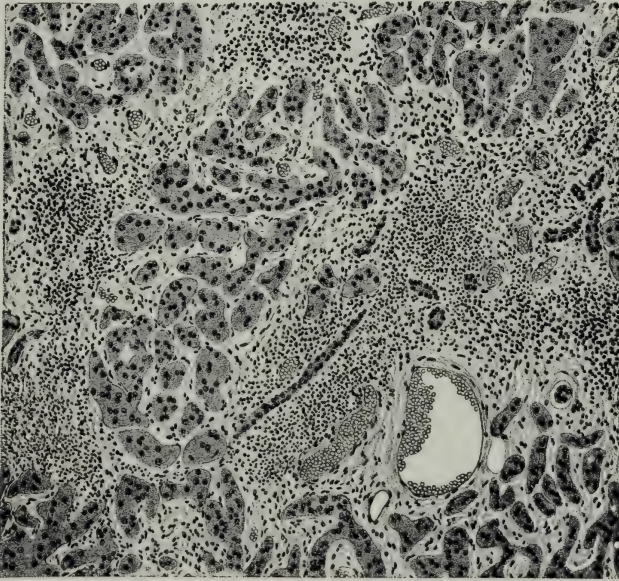


FIG. 298—An area of cirrhosis in which perilobular infiltration of lymphoid cells is marked.

as cloudy swelling, hemosiderin pigmentation, edema and fibrosis. The effect in the peritoneal cavity is ascites. In uncomplicated cases the fluid is colorless, or pale yellow, limpid, poor in solids and in cells. After repeated paracentesis the specific gravity may be greater, the number of cells greater, the color darker and adhesions may form between neighboring peritoneal surfaces. It is usually believed that ascites is of essentially mechanical origin, but Roger maintains that cirrhosis is a "hydropogenic" disease leading in many cases to a generalized edema such as occurs in Bright's disease; in his view ascites is a manifestation of this general tendency perhaps induced locally in the peritoneum by the passive hyperemia. Although anal hemorrhoids are not frequent, the dilatation of veins at the lower end of the esophagus, the so-called esophageal hemorrhoids, is of importance and may by rupture lead to severe or fatal hemorrhage. If adhesions form between the liver and abdominal walls the drainage of the portal circulation may be improved. Commonly,

however, collateral circulation is provided by enlargement of veins which can carry the blood from the portal area directly to the thorax without passing through the liver, communicating ultimately with either the inferior or superior vena cava. The various possibilities are completely outlined by Roger. The superficial abdominal veins may partake in this process and show lines from the groin toward the umbilicus and thence up toward the chest. Marked venous enlargement around the umbilicus is referred to as the *caput Medusæ*. The obstruction to portal blood flow is shown in increased portal pressure. This may be due to limitation of the portal bed within the liver by the perilobular fibrosis, or as Herrick suggests, in studies as yet unconfirmed, to alterations in pressure relations between hepatic and portal circulation,

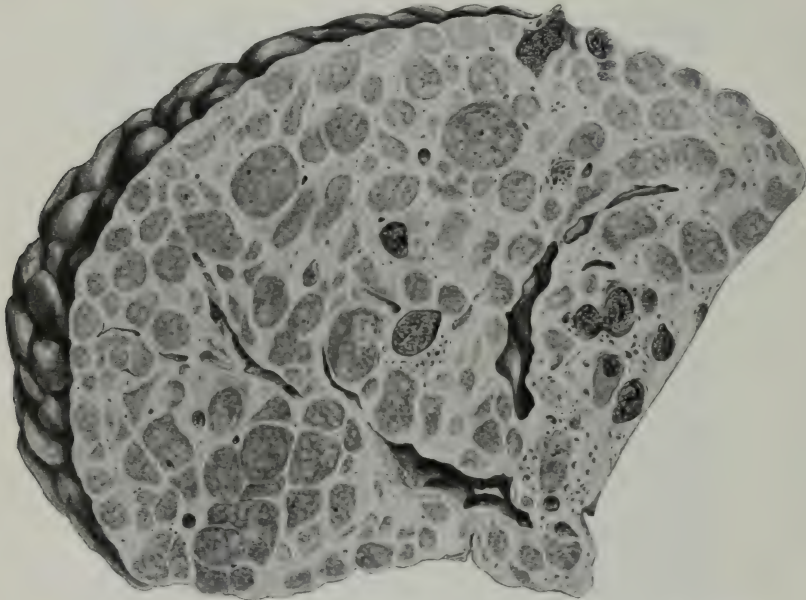


FIG. 299—Cut surface of liver in atrophic cirrhosis. Note the large sharply defined parenchymatous nodules, evidently the result of multiplication of liver cells producing the pseudo-adenomatosis of the liver.

whereby arterial pressure, communicated more directly than normal to the portal system, increases the pressure in the latter.

Obstructive Biliary Cirrhosis.—The result of prolonged stagnation of secretion of a gland is usually atrophy of the secreting substance and overgrowth of supporting connective tissue. Experimentally, at least, as shown by Richardson, this occurs in the liver as the result of prolonged obstruction to the hepatic duct. After several weeks, rabbits show an obstructive biliary cirrhosis which resembles very closely an atrophic cirrhosis with extreme jaundice. It is probable that this process conforms closely to that in other glands. In human medicine obstructive biliary cirrhosis is uncommon, partly because modern surgery relieves the obstruction, and partly because the various changes incident to prolonged stagnation of bile lead to death before cirrhosis appears. Nevertheless, occasional cases are observed in which

there is partial or almost complete obstruction to the outflow of bile as the result of calculi or tumors, in which there occurs a cirrhosis which grossly resembles very closely atrophic cirrhosis with the addition of jaundice. Histologically, the picture is much the same except for the accumulation of bile pigment in the biliary capillaries and canaliculi within the cells. In addition the smaller bile passages in the perilobular connective tissue may be infiltrated with or surrounded by lymphocytes, plasma cells and sometimes polymorphonuclear leucocytes. This inflammatory infiltrate is interpreted by Mallory to indicate that infection must be present in addition to the bile stagnation, but until convincing bacteriological proof is brought forward it remains at least possible that the presence of the stagnant bile may result in this low grade cholangitis. It is also likely that the cause of the stagnation may provide a focus of entrance for infection, and the latter may thus be secondary to the stagnation and not in any sense a primary cause of the fibrosis.

Perilobular Fibrosis.—It is not uncommon to find in advanced life an amount of perilobular connective tissue which apparently is in excess of that considered normal for younger individuals and those of middle life. In chronic intoxications such as that of lead poisoning and in chronic infections, more particularly tuberculosis and syphilis, such perilobular fibrosis may slightly roughen the surface of the liver and be apparent as a fibrous network in the cut surface. Histologically, the overgrowth may be greater in patients with tuberculosis than in others, as shown by Lavenson and Karsner, associated with slight multiplication of bile ducts and infiltration of small mononuclear cells. The dividing line between such slight or moderate perilobular fibrosis and a true atrophic cirrhosis, is in some instances difficult to draw and often remains a matter of personal opinion. It is possible that such fibrosis may be the early stage of an atrophic cirrhosis. In the stage under discussion the condition undoubtedly has little or no functional significance.

Capsular Pseudocirrhosis.—Fibrosis of the capsule of the liver occurs in syphilis and other chronic infections and is especially prominent in cases of so-called multiple serositis, in which the fibrosis is likely to involve also the splenic capsule, pleura and pericardium. There is sometimes an extension of the capsular fibrosis into the substance of the liver along the lines of the perilobular connective tissue. In the involved areas the parenchymatous substance is usually reduced, but it is rare that retraction of the connective tissue occurs so as to lead to nodularity of the organ. The extension is rarely more than one or two centimeters into the liver, and is not regarded as a true cirrhosis since it is not widely disseminated through the organ.

Central or Cardiac Cirrhosis.—This condition has been discussed in connection with passive hyperemia in the liver. The liver is reduced in size and firmer than normal. Rarely, if ever, is there any evidence of nodular character. While it is possible that the passive hyperemia leads to some increase in the connective tissue around the central veins, it is also safe to assume that in many cases this is merely a relative matter, the connective tissue becoming

more prominent because of atrophy and even necrosis of the central parenchymatous cells. This should be regarded as an atrophic stage of chronic passive hyperemia, a red atrophy, rather than a true cirrhosis.

Hypertrophic Biliary Cirrhosis.—This was described in 1876 by Hanot who spoke of it as biliary hypertrophic cirrhosis with chronic icterus. It is apparently more common in France than elsewhere, is of insidious onset, as a rule shows tremendous enlargement of the liver and great enlargement of the spleen. Jaundice is apparently due, as suggested by Eppinger, to obstruction in the finest biliary passages. It is not complete and the stools are not acholic. The formation and destruction of bile are probably not interfered with since there is usually no urobilin in the urine. Intermittent fever is commonly observed. The cause of this variety of cirrhosis is even more mysterious than that of atrophic cirrhosis. Castaigne, while admitting that certain infections as malaria, tuberculosis, scarlet fever, typhoid fever and

also alcoholism, may rarely cause the condition, believes that syphilis is the outstanding etiological agent because of finding positive Wassermann tests in many instances. It is, however, possible that syphilis may accompany and not necessarily cause the disease.

Grossly, the liver is considerably enlarged attaining a weight of as much as five kilograms. The capsule is tense, the edges rounded, the organ firm and of yellow or greenish-yellow color. It cuts with increased resistance and shows a more or less retracting, firm, uniformly fibrosed cut surface with little or no lobular distinction. Histologically, the jaundice

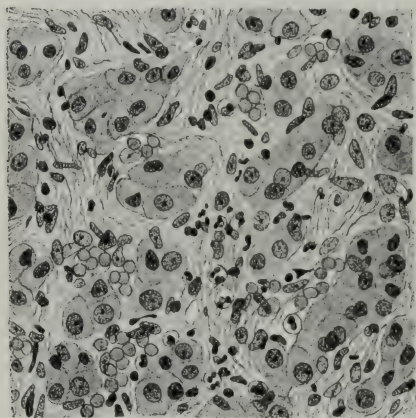


FIG. 300—Intra-lobular fibrosis in hypertrophic cirrhosis of liver, separating the liver cords.

may or may not be apparent in the form of solid masses of pigment. Fibrosis is moderate in the perilobular connective tissue, but reaches extensively between the liver cords, a feature which distinguishes this disease from the perilobular fibrosis of the other forms of cirrhosis. Bile duct proliferation may or may not be prominent as is true also of infiltration of small mononuclear cells. This conception of hypertrophic cirrhosis is that originally given by Hanot, but subsequent publications of his own and of others have confused the picture, so that some now regard as hypertrophic biliary cirrhosis a large liver with fibrosis limited to the perilobular connective tissue and associated with jaundice. As pointed out by Eppelen, Heineke considers a diffuse capillary cholangitis as an essential part of the picture. The latter regards the cause as infectious, and states that passive hyperemia in the portal circulation does not occur because there is little or no tendency for the connective tissue to contract. "Doubtless many cases of Laennec's cirrhosis with enlarged liver are erroneously described as being of Hanot's type."

Syphilis.—Congenital syphilis may or may not lead to anatomical lesions, but if fatal in early life, the liver with or without coarser lesion, is likely to show large numbers of *treponema pallidum*. Definite lesions are likely to be of one or two forms, probably essentially dependent upon failure of the parenchyma to develop completely. Thus, there may be in the perilobular spaces a mass of round cells presumably representing mesoblast, or there may be a mass of adult connective tissue somewhat resembling atrophic cirrhosis, associated with lymphoid and plasma cells, increased number of the bile ducts and distortion of lobules. In the other important form there is a more diffuse growth of fibrous tissue within the lobules, surrounding capillaries and sinusoids, separating and distorting the liver cords. Grossly, the liver may be large, normal in size or small, is usually firm and sometimes shows slight nodularity of the outer surface and cut surface, especially when the fibrosis is marked in



FIG. 301.—The liver in syphilitic cirrhosis, *hepar lobatum*.

the perilobular spaces. In either form of fibrosis, small areas of focal necrosis may be frequent or there may be multiple miliary gummata. It is at least possible that the focal necroses represent the early stage of miliary gumma formation. Uncommonly, large gummata are observed.

Acquired syphilis affects the liver in a variety of ways. In the secondary or even tertiary stage of syphilis jaundice may occur, presumably due to degenerative lesions of the liver cells or perhaps acute parenchymatous inflammation (Whitcomb). According to Flexner, chronic perihepatitis is by no means uncommon. It occurs as a thick fibrosis of the capsule of the liver, often hyalinized, occasionally calcified, and is usually associated with adhesions. This may result in the so-called capsular cirrhosis. Many observers are of the opinion that a perilobular fibrosis diffuse in extent, and often progressing to more or less marked atrophic cirrhosis, occurs in syphilis. This is of the nature of the generalized fibrosis in late syphilis. It is at least possible that some patients who show the signs of early atrophic cirrhosis and who recover under

treatment are victims of this type of lesion. Gummata may occur in the substance of the liver or project as nodular masses above the surface of the organ. They may be single or multiple and may attain a diameter of 5 cm. or more. They are distinguished by a fairly solid necrotic content and dense fibrosis in the margin.

Great distortion of the liver may occur as the result of contraction of scar tissue in radiating lines around gummata in the substance of the organ. Thus, the outer surface is broken up into many smaller lobes, producing the so-called *hepar lobatum*. The intervening liver substance may be apparently normal, the seat of a perilobular fibrosis or a mild atrophic cirrhosis. Section of the liver shows the radiating lines of connective tissue communicating centrally with the remains of a gumma, or sometimes a nodule definitely distinguishable as a gumma, and peripherally with the retracted parts of the liver surface.

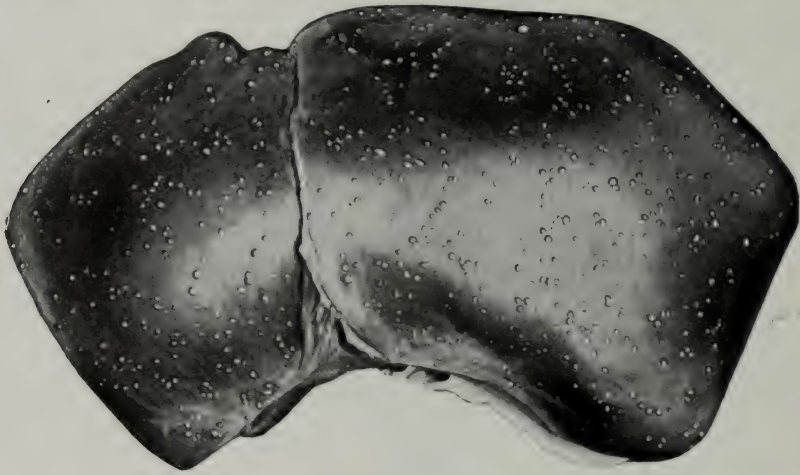


FIG. 302.—Miliary tuberculosis of the capsule of the liver.

Histologically, the small arteries in the neighborhood of the dense areas of connective tissue may show chronic obliterating or deforming endarteritis. The masses of connective tissue are often infiltrated with lymphoid or plasma cells, and may occasionally show multiplication of bile ducts. Amyloidosis of the liver may be caused by syphilis. The subject of congenital and acquired syphilis of the liver is admirably reviewed by Herxheimer.

Tuberculosis.—There are three important forms of tuberculosis of the liver. Miliary tuberculosis of the liver is common in generalized miliary tuberculosis. Often the miliary tubercles are not visible to the naked eye but are found upon histologic examination, occupying principally the perilobular connective tissue. Under these circumstances they are usually extremely small and composed only of endothelial and lymphoid cells with relatively few giant cells and little or no necrosis. Such grossly invisible tubercles may be assumed to be present in most cases where there is hematogenous miliary tuberculosis involving lungs, spleen and kidneys. Small conglomerate tubercles may be visible grossly as minute gray points or larger miliary tubercles, one or two

millimeters in diameter. Microscopically, these are found to be either large miliary tubercles with central necrosis or small conglomerate tubercles. Conglomerate tuberculosis of the liver may be secondary to pulmonary tuberculosis or to abdominal or even genito-urinary tuberculosis. There may be several foci attaining a diameter of about seven millimeters or more, or rarely there are large solitary tubercles with a diameter of several centimeters. The latter may show a fibrous wall and must be differentiated from gumma, usually by means of staining for the tubercle bacilli. The third form which is uncommon, is characterized by involvement of the biliary passages, and bile staining of the content of the tubercles. It is sometimes named *tuberculous cholangitis* or pericholangitis. The liver shows tuberculous masses varying from a few millimeters to a centimeter or more in size, usually clearly defined and containing bile stained, cheesy material. Occasionally, secondary infection occurs producing abscesses. The condition is more frequent in connection with tuberculosis of the abdominal cavity. According to the studies of Winternitz, such a process may arise by invasion of the intrahepatic bile ducts by caseous tubercles in the perilobular connective tissue, or may be due more rarely to an ascending tuberculous infection of the biliary passages. As has been mentioned above, perilobular fibrosis of the liver is more common in victims of tuberculosis than in non-tuberculous individuals of the same age group. Certain authorities regard tuberculosis as a possible cause of atrophic cirrhosis of the liver, but this cannot be accepted as final, and it is at least possible that alcoholism or some other associated condition is more directly the cause than is the tuberculosis. Amyloidosis of the liver may occur in connection with direct tuberculous infection of the organ.

Actinomycosis is not rare in the liver and may be observed secondary to intestinal actinomycosis and due to extension either directly or through the retroperitoneal tissue. It may also be metastatic from actinomycosis in more distant parts of the body.

Lymphomatous Nodules.—Since there is presumably lymphoid tissue in the liver normally, it is to be expected that diffuse disease of the lymphoid apparatus will be observed also in the liver. Thus, in lymphatic leucemia it is not uncommon to find grossly visible, pale gray nodules representing the rich infiltration of lymphoid cells in the perilobular spaces. The same is true sometimes in lymphosarcoma. Hodgkin's disease can also affect the liver in this fashion. These conditions have been discussed in the chapter on hematopoietic system.

Tumors.—The commonest tumorous condition of the liver is the cavernous hemangioma, sometimes called cavernoma. This is a very common incidental finding at autopsy, especially in adults. The cavernoma may be single or multiple, usually situated immediately under the surface of the liver and varying in size from a few millimeters to several centimeters. It is a well-defined purple or dark blue mass, which bleeds freely and retracts somewhat below the cut surface of the organ. When the blood is washed out, the mass has a somewhat spongy appearance. Microscopically, it is made up of an interlacing

network of dense connective tissue enclosing fairly large spaces lined with endothelium and filled with blood. It may or may not be definitely encapsulated and sometimes shows connection between the blood spaces and the sinusoids of the liver. Characteristically, the cavernous hemangioma is benign both pathologically and clinically, but rare cases occur in which the tumor becomes locally invasive. We have observed one case in which the liver weighed more than sixteen kilograms, due to extensive invasion of a cavernous hemangioma. Since the condition occurs more frequently in adults than in children, it is assumed by some that the spaces represent dilatation of sinusoids with disappearance of liver substance. On the other hand, the condition has so much in common with the hemangiomata of the skin that it is regarded as of congenital origin. In this sense it is looked upon as a hamartoma which, when it undergoes true tumor formation, becomes a hamartoblastoma. It may rarely be associated with similar lesions in other organs (Moise).

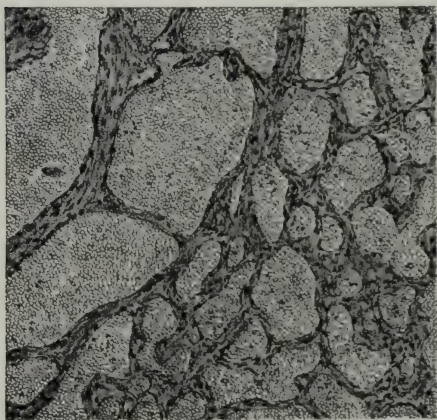


FIG. 303—Cavernous hemangioma of the liver.

probably representing a multiplication of bile ducts. Both the liver cell adenoma and the tubular biliary adenoma may secrete bile. In the former it appears as masses of pigment within or near the cells and in the latter may so distend the spaces as to produce a cystadenoma.

Adrenal inclusions are sometimes observed and we have seen one case of hypernephroma. Fibrolipoma and fibroneuroma are said to occur.

Carcinoma.—Carcinoma may be primary or secondary in the liver. Primary carcinoma is an uncommon but by no means rare disease. It has been studied by a large number of investigators including particularly Eggel, Winternitz, Jaffe, Karsner and others. It occurs more frequently in men than in women, is seen most frequently in the fourth and fifth decades of life, and very often is accompanied by a history in which some of the presumptive etiological factors of cirrhosis of the liver are found. Eggel differentiates three forms grossly. In the nodular form there are numerous nodules variable in number and size, usually clearly separated from the liver tissue. In the massive form the tumor constitutes a large mass occupying either an entire lobe

Adenoma of the liver is relatively uncommon. The growth may be single or multiple. The size varies from a few millimeters to several centimeters. The tumor may bulge slightly above the outer surface, and in cut section is soft, bulging, light yellow, or brown in color and distinctly friable. It is well-defined, compresses the surrounding liver substance and is sometimes encapsulated. Microscopically, the tumor cells resemble liver cells, irregularly arranged but sometimes with interlacing capillaries between cell cords. It may, however, be tubular or acinar in character

or the greater part of it. It is poorly defined and shows neighboring small secondary nodules. In the diffuse form the whole liver is infiltrated with numerous small tumor nodules often no larger than an acinus, each enclosed in a connective tissue band so that the lesion is only differentiated from a true cirrhosis by the aid of a microscope. It is important to note that in all of these forms the tumor appears as a distinctly invasive and not compressive growth. Cirrhosis accompanies most cases of primary cancer, and jaundice is present in the majority of cases.

Microscopically, two forms are to be distinguished, namely, the carcinoma solidum and the carcinoma adenomatosum. The former is usually a carcinoma simplex and by many is supposed to represent a tumor originating from liver

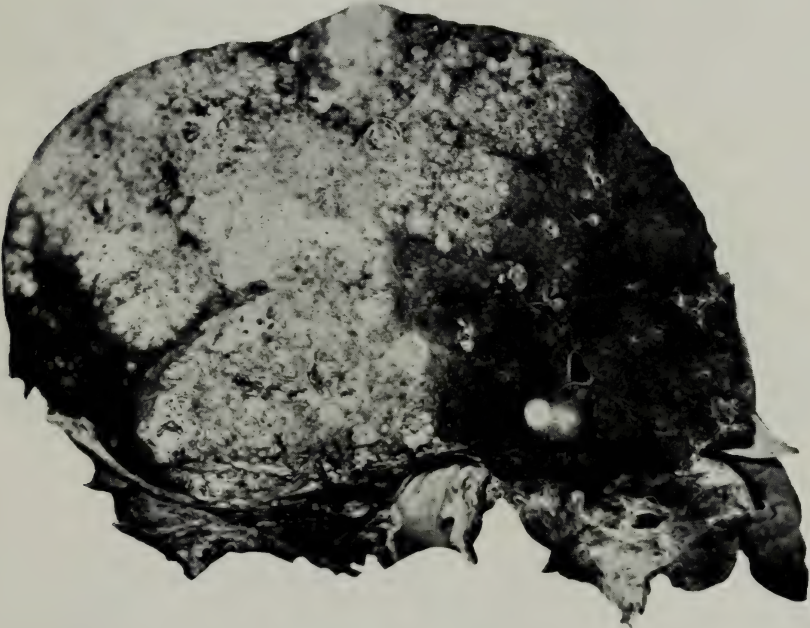


FIG. 304—Massive primary carcinoma of liver.

cells. This, however, cannot conclusively be stated. The adenomatous form is more truly a tubular form, apparently representing bile duct proliferation, although this is no positive assurance that such tumors originate in the bile ducts. The tumor is invasive and may show bile pigmentation histologically. Many cases show early symptoms suggesting those of cirrhosis and this is often interpreted (see Jaffe) to indicate that cirrhosis precedes the carcinoma. Ascites, edema of the lower extremities, splenic enlargement and more rarely fever present themselves in a variable number of cases. Cirrhosis is an associated condition in almost all cases. Tumor thrombosis of the intrahepatic blood vessels is common and intrahepatic metastases are frequent. Extrahepatic metastases are more common and more widespread than usually is believed. Their distribution, together with the frequent presence of tumor thrombosis of the intrahepatic blood vessels, leads to the conclusion that

the transmission of the condition to other organs is largely through the blood vascular system. Thus, metastasis in the lungs is the most common form.

Secondary carcinoma of the liver is most frequently metastatic from the stomach, but may invade the liver from other parts of the alimentary canal, the organs of the abdominal and pelvic cavities, the respiratory tract, the skin, breast and other situations. Grossly, the nodules may be multiple or single, usually the former. When multiple, they present a greater degree of uniformity in size than is true of the multiple nodules of primary carcinoma. They grow rather by a combination of invasion and compression and are accordingly more sharply defined than is true of primary carcinoma. Jaundice is less frequent in secondary than in primary carcinoma, and cirrhosis is also less frequent and is to be regarded as an incidental finding. The nodules are often pale gray or pale yellow in color, soft, bulge in the cut surface and show early

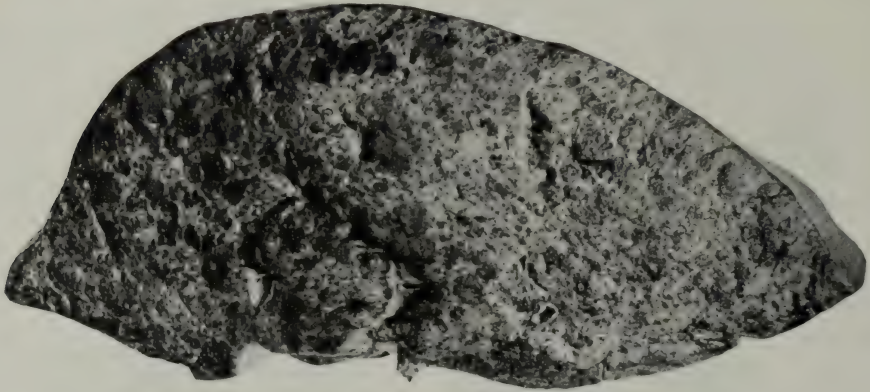
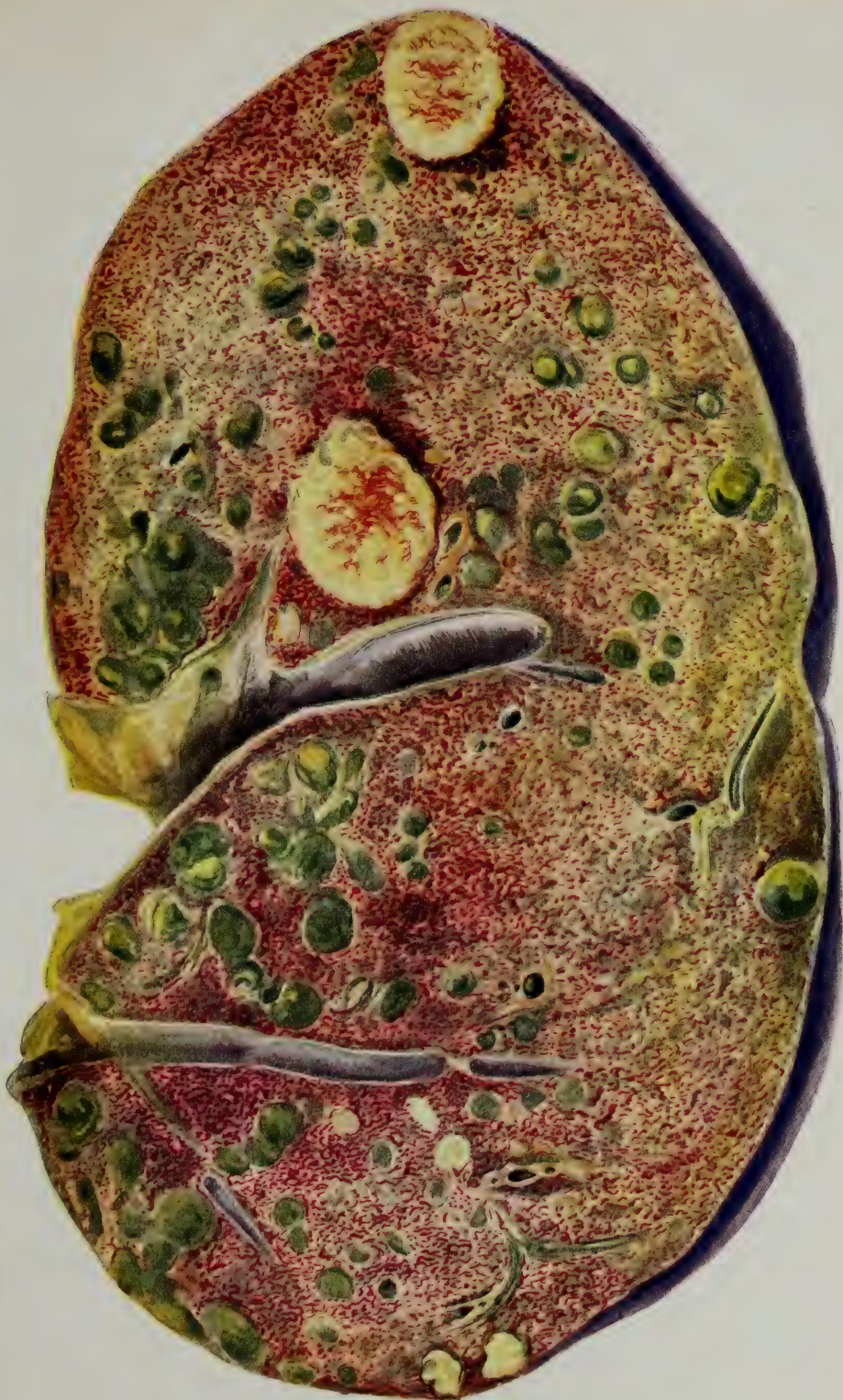


FIG. 305—Multiple nodules of metastatic melanotic sarcoma in the liver.

necrosis. Nodules in the outer surface, after they have undergone central necrosis, show commonly a central depression, the so-called umbilication.

Sarcoma.—Primary sarcoma is rare and may occur as single or multiple nodules. Spindle cell sarcoma, round cell sarcoma and various subvarieties are described. The hemangio-endothelioma is probably also to be included in the group of malignant connective tissue tumors (Veeder and Austin). Sarcoma appears also to be associated with cirrhosis of the liver (Jaffe). Experimentally it has been produced by infection with *cysticercus fasciolaris* (Bullock and Curtis). The round cell forms may represent some variety of lymphosarcoma. The spindle cell forms may possibly be confused with spindle cell formation in carcinoma, in which, as in the thyroid, the reactionary connective tissue growth may lead to elongation of the epithelial cells. Any form of sarcoma, primary in other situations, may show metastases in the liver. Outstanding among these is the pigmented sarcoma of the choroid coat of the eye, which apparently produces metastasis in the liver more often and to a greater extent than in other organs. Extensive infiltration of the liver may also occur as secondary to malignant transformation of pigmented moles of the skin.

PLATE XIX.—Drawing of nodules of secondary carcinoma of liver. The smaller nodules are icteric; the larger ones show necrosis of the central parts.



Cysts.—Experimentally, McMaster and Rous have shown that obstruction to the bile passages may lead to wide distention of the duct, without ballooning of the organ itself, a hydrohepatosis. The failure of marked enlargement of the liver is attributed to the low secretory pressure. In man local distention may become cystic in character, particularly as the result of cicatricial obstruction to preëxisting bile ducts within the liver, or to secretion within newly formed bile ducts without sufficient outlet. Such cysts are usually small, multiple, occur within the substance of the liver and may contain bile or colorless secretion. More common are multiple cysts immediately under the capsule of the liver, variable in size, projecting above the surface, thin-walled, and usually containing clear limpid fluid. Occasionally a thicker viscid fluid or even bile may be observed. The cysts are usually lined with cylindrical epithelium but occasionally ciliated epithelium or flat epithelium is seen. This appearance is commonly associated with congenital cyst-adenoma of the kidney, and is believed to be due to a congenital fault in the development of the bile passages. Lymphatic cysts have been described. The commonest cyst in the liver is the echinococcus cyst.

Parasites. Echinococcus Cysts.—Infestation of man by this parasite occurs more frequently in central and north-

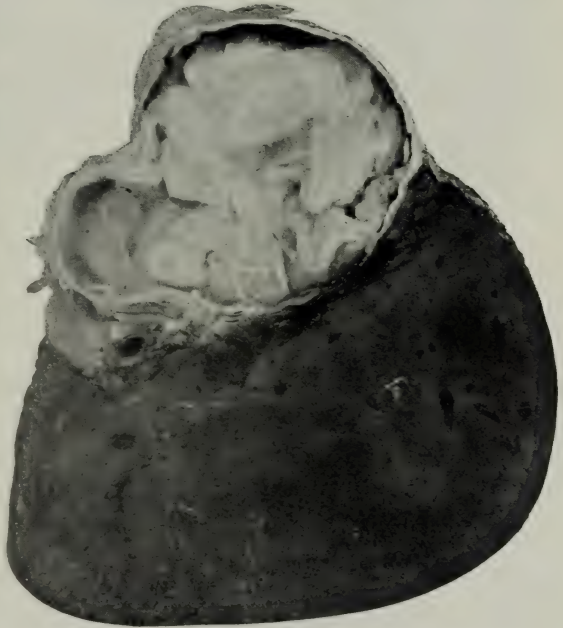


FIG. 306—Echinococcus cyst of liver. Army Medical Museum 12072.

ern Europe than elsewhere, and sporadic cases in this country are almost invariably in individuals who have migrated from those parts of the world. The fœtia echinococcus occurs in large numbers in the gut of the dog. The worm measures about 6 mm., the head and neck being about 3 mm. in length and accompanied by three or four small segments or links. The ova (embryophore) contained in the feces of the dog, may be taken into the intestinal canal of man and a wide variety of other animals. The hexacanthus embryo hatches in the stomach or intestine, bores through the gut wall and is conveyed by either blood or lymph stream to almost any part of the body. This mode of entry predisposes the liver to infestation. In the liver, as in other organs, there is subsequently formed a slowly growing cysticercus or larval stage. The fully developed cyst shows a wall made up microscopically of concentric laminæ of hyaline chitinous-like

material, and is lined by the "germinal cells" from which grow "daughter" cysts and in turn "granddaughter" cysts and so on in the same fashion. The parent cyst may grow to great size. The daughter cysts vary in size from a



FIG. 307—Multilocular echinococcus cysts of liver, showing the usual extensive fibrosis of the organ and the shaggy lining of the cyst walls.

few millimeters to a centimeter or more and often are free in the larger cyst. Their walls are thin and translucent. A low grade chronic inflammatory reaction about the parent cyst leads to the formation of a fibrous capsule. The

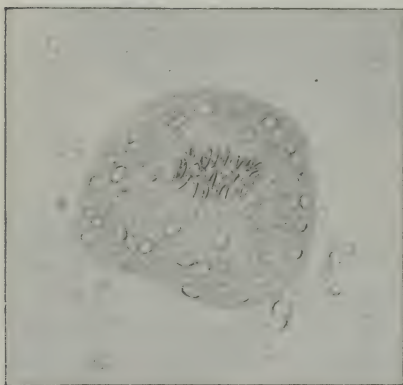


FIG. 308—Scolex and hooklets recovered from fluid of echinococcus cyst.

cyst content is usually a thin, limpid, colorless fluid, of low specific gravity, containing salt, very little protein, cholesterol, creatin, sometimes sugars, presumably derived from glycogen, and other substances. It is irritant to the skin and is said to be toxic for animals. Rupture into the peritoneum may be followed by inflammation, intoxication and even death (Wells). Used as an antigen, the fluid shows precipitin reactions and complement fixation with the patient's serum. The fluid contains scolices, or more often free hooklets, and may be the source of secondary cysts. In old cysts the fluid may

become inspissated and of putty-like character, in which stage daughter cysts, scolices and hooklets are often absent. Rarely, instead of this endogenous formation of daughter cysts, exogenous formation may lead to a more or less focal collection of cysts.

The so-called multilocular echinococcus cyst is rare as a primary condition.

It invades the liver widely producing cysts of variable size, the larger ones showing a rough, shaggy wall. The contents are often gelatinous in character, the whole condition sometimes resembling mucinous carcinoma. The intervening liver is fibrosed and may show extensive bile duct multiplication. It is believed that this is due to a slightly different worm, the *tenia multilocularis*, peculiar in larger scolex, larger number of segments, arrangement of uterus and most especially in its disposition to produce the multilocular cyst in its larval stage.

Pentastomum denticulatum, the larval stage of *pentastomum tenioides*, occurring in the nose of dogs, forms multiple minute nodules in the human liver, sometimes fibrous and more often calcified. Invading more especially the biliary tracts and exciting inflammation in the peribubular connective tissue, occasionally with abscess formation, are rare infestations by *fasciola hepatica*, *dicrocoelium lanceolatum*, *opisthorchis felinus*, *clonorchis sinensis*. *Ascaris lumbricoides* may occur in the larger bile passages and produce icterus (Motta). *Coccidium oviforme* produces papillary proliferation of the biliary passages very commonly in the rabbit and is said to occur in man.

Foreign bodies may be encountered in the liver as the result of wounds or from penetration through some part of the intestinal canal.

GALL BLADDER AND BILE DUCTS

Congenital Anomalies.—The gall bladder may be congenitally absent. It may show a longitudinal fissure sometimes deep enough to divide it into two bladders, even with separate ducts. It may show an hourglass form due to transverse fissure. It may lie under the left lobe. It may be embedded in the substance of the liver or may more rarely be entirely separate as a “floating” gall bladder.

Various abnormalities are found in the union of the two main hepatic ducts with each other and with the cystic duct. The common duct may be very short and is sometimes double. It may show abnormalities of union with the pancreatic ducts. The papilla may be double or may be situated high in the duodenum. In congenital absence of the gall bladder the common duct may show cystic dilatation.

Congenital atresia of the bile ducts is of considerable clinical importance. It may affect any part of the hepatic, cystic or common ducts. The affected parts may be solid cords or entirely absent. The gall bladder may be absent, rudimentary or dilated. Howard and Wolbach review the theories as to the origin of the condition, and conclude that no one theory will explain all the cases. Some may be due to faulty development of the passages. Others may be due to inflammation in fetal life. Others may be the result of a downward extension of the inflammatory process from a primary congenital cirrhosis of the liver.

Retrogressive Changes.—Passive hyperemia and edema may result from general passive hyperemia or that of liver cirrhosis. Minute hemorrhages may occur under these circumstances or may accompany inflammations. Necrosis

and gangrene may occur in the rare cases of "floating" gall bladder, when it twists upon the duct. Atrophy may follow chronic inflammations.

Inflammations.—The cause of inflammation may enter the gall bladder either from the duodenum or by way of the portal circulation, occasionally through the general circulation as in pyemia, sometimes through lymphatics from neighboring inflammation, and rarely as a direct invasion from inflammation of the peritoneum. Nichols emphasizes the probability that in typhoid, cholera and dysentery the organisms are carried into the liver by the blood stream and thence into the gall bladder. The commoner bacteria involved, according to Posselt, include, in the order of frequency, colon bacilli, typhoid bacilli, paratyphoid bacilli and streptococci. More rarely are found staphylococcus, dysentery bacillus, pneumobacillus of Friedländer, bacillus pyocyaneus, bacillus influenzae, the anaërobic gas bacilli and bacillus proteus. The acute

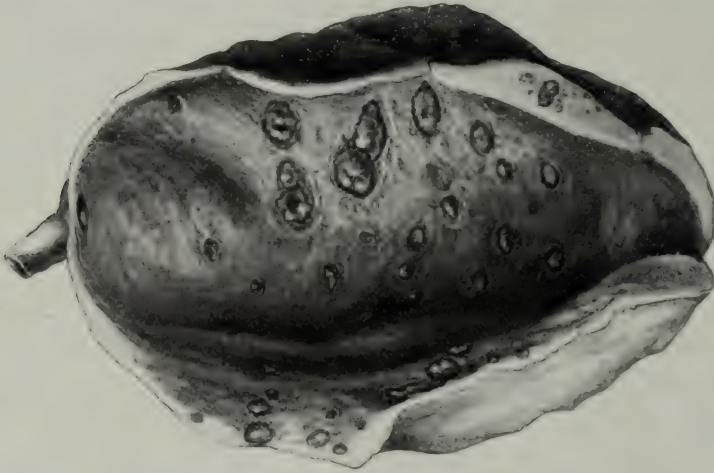


FIG. 309.—Acute ulcerative cholecystitis.

inflammations are particularly catarrhal, suppurative, or pseudomembranous. The chronic inflammations may be catarrhal, may be chronic suppurative or pseudomembranous forms, and may be a chronic ulcerative type.

Acute Catarrhal Inflammation.—This affects most frequently the common duct, as the result of an extension from a catarrhal inflammation of the duodenum. It is unusual for such an inflammation to extend as far as the gall bladder. The jaundice produced by the plugging of the orifice, either by swelling or accumulation of mucus, is commonly referred to as catarrhal jaundice and usually disappears in the course of a few days. More severe catarrhal inflammation may result from obstruction to the outlet of bile, and infection with organisms such as bacillus coli communis. Poisons such as phosphorus and arsenic may produce catarrhal inflammations of the intrahepatic ducts. Catarrhs also accompany various infectious diseases, particularly typhoid fever, cholera and smallpox. When seen at autopsy catarrhal inflammation is usually an incidental finding. The mucosa is red, swollen, and covered with gray, viscid mucus. Microscopically, there is cloudy swelling and sometimes

mucinous degeneration of the epithelium, hyperemia, edema and infiltration of mononuclear cells and a few polymorphonuclear leucocytes.

Acute Suppurative and Fibrinous Inflammations.—The acute suppurative form usually originates in ulcers, which may be secondary to fibrinous inflammation, to chronic ulcerative forms, or to the erosion by gall stones. The suppuration may become extensive, producing a phlegmonous type of cholecystitis or cholangitis. Local inflammation of the surrounding peritoneum may occur; sometimes there is direct invasion of the liver by the abscess; or there may be extension along the intrahepatic bile ducts with the production of multiple abscesses. If the outlet of the gall bladder be obstructed, pus may accumulate within the gall bladder, producing the so-called empyema of the gall bladder. The acute fibrinous forms are often combined with ulcer formation. The ulcer may erode into blood vessels with subsequent hemorrhage, or may perforate through the gall bladder to produce local or general suppurative peritonitis.

Chronic Inflammations.—These may follow any of the acute forms. In the usual chronic catarrhal inflammations of the gall bladder there is distention of the ducts of the bladder with thinning of the walls. Often the content is a thin, only slightly viscid, clear brown or colorless fluid. More especially in older persons the chronic catarrh may be accompanied by papillary outgrowth from the lining mucosa. On the other hand, the chronic catarrh as well as the acute suppurative and fibrinous inflammations, may lead to a chronic productive or fibroplastic type of inflammation in the entire wall of the gall bladder and ducts, which become considerably thickened due to fibrosis of all the coats. The contraction of the fibrous tissue may produce interlacing trabeculation of the lining of the gall bladder. As the process continues the gall bladder is reduced in size and finally may show an extremely small cavity. Sometimes the fibrosis is followed by calcification and even ossification. Accompanying the condition there is likely to be a productive pericholecystitis and pericholangitis with adhesions to the surrounding structures. Of somewhat the same type is chronic ulcerative cholecystitis which differs principally in that there are numerous ulcers in the lining membrane. Such a form is usually accompanied by gall stones, single or multiple, and is of considerable importance because of the possibility that it may lead to acute suppurative cholangitis.

Infectious Granulomata.—These are rare. Gumma may occur in the gall bladder in either congenital or acquired syphilis, and lead to stenosis or obliteration. Tuberculosis may enter the gall bladder from neighboring tuberculous lymph nodes or the organ may be involved in a generalized miliary tuberculosis. In the more extensive cases, tuberculous ulcers are found in the mucosa, identified bacteriologically. Actinomycosis occasionally involves the gall bladder from intestinal canal or liver.

Cholelithiasis.—The composition of biliary concretions and the mechanism of their formation have been discussed in the chapter on mineral infiltrates and concretions. As judged by clinical manifestations, cholelithiasis occurs most commonly, according to Chauffard, between the ages of thirty and

fifty-five years, although it may occur at any period of life. It is much more frequent in women than in men and occurs especially during and after pregnancy. There appears to be a familial disposition to the disease, but it is not conclusively demonstrated as hereditary. The most characteristic sign of the presence of concrements is biliary colic, but some cases give only manifestations of irritation or inflammation of the gall bladder and others are entirely symptomless. From observation of gall bladders obtained at operation and at autopsy, it may be said that concrements may produce no lesion of the gall

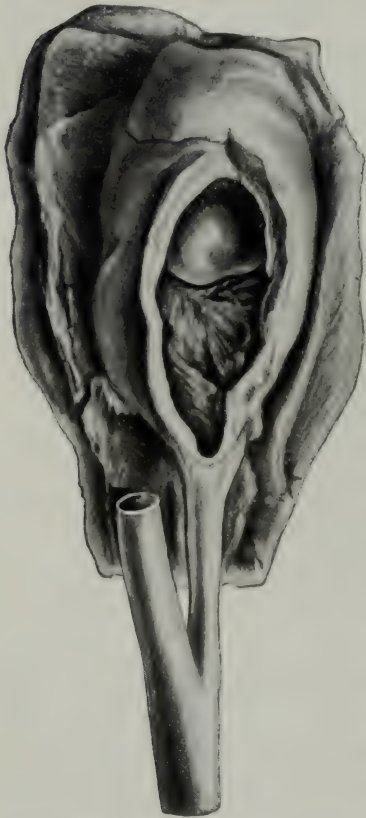


FIG. 310—Cholelithiasis.

bladder. This appears to be especially true of the multiple faceted concrements. There may be merely a slight catarrhal inflammation of bladder and ducts. As pointed out by Rost, the sphincter of Oddi does not prevent entry of bacteria from the intestinal canal, and such an irritative catarrh may predispose to inflammations of greater severity, as have been described above. When stones are lodged near the neck of the gall bladder for a considerable period, local atrophy with fibrosis and possibly constriction, may occur. Similarly ulceration may ensue, with such possible dangerous sequels as suppurative inflammations or perforation. Often the point of perforation is protected by adhesions so that there is local abscess formation, but occasionally the concrement and other contents of the gall bladder enter the peritoneum with resultant generalized acute peritonitis. Lodgment of the concrement in the cystic duct may produce wide distention of the gall bladder. Lodgment in the common duct may produce jaundice, in prolonged cases obstructive biliary cirrhosis, and if associated with infection, extensive intrahepatic cholangitic multiple abscesses.

The prolonged irritation of gall stones may result in cancer. Concrements entering the intestinal canal usually pass out in the feces, but rarely may produce intestinal obstruction.

Obstruction of Bile Ducts.—This may occur within the liver by tumor invasion or by contraction of fibrous tissue. Obstruction of the extrahepatic ducts may be due to acute inflammations, concrements, foreign bodies or parasites, tumors within or outside the ducts, enlarged lymph nodes and by the contraction of scars in the duodenum or of peritoneal adhesions. Following obstruction of the hepatic duct or its intrahepatic tributaries there is general icterus. If the obstruction be prolonged the ducts may be much dilated (hydrohepatitis) and even though icterus continue, the bile is gradually replaced

by a thin, colorless, clear or slightly cloudy fluid, the secretion of the ducts. According to Rous and McMaster the fluid is secreted under considerable pressure, is alkaline, of low specific gravity and practically devoid of choleates and cholesterol. If the cystic duct be obstructed, there is probably at first a reduction in size of the gall bladder due to the resorptive capacity of the wall, but ultimately there is wide distension due to the secretion by the mucous membrane. The fluid within the gall bladder is usually of much the same character as that in the ducts, except that it is more viscid because of the larger amount of mucus. This is called hydrops of the gall bladder or hydrops cystidis felleæ. The wall is usually thin and the muscle atrophic, or there may be chronic inflammation. Rupture is rare. Obstruction of the common duct produces much the same changes as those of hepatic duct obstruction, but usually less distention of the gall bladder than is seen following obstruction to the cystic duct.

Tumors.—Among the unusual tumors of the gall bladder and the larger bile ducts are included the papilloma, which is sometimes diffuse, fibroma, adenoma, sometimes simple and sometimes diffuse, adenofibromyoma, myxoma, and mixtures of these with other types of tumor. The sarcoma is distinctly unusual but occasional cases are reported. Carcinoma of the gall bladder is fairly frequent and involves especially gall bladders which contain concretions. It is usually assumed that the irritation of the concretions leads indirectly to the establishment of the carcinoma. Although

occasionally the carcinoma is limited in extent and projects into the gall bladder as a cauliflower-like mass, nevertheless, as a rule, it is a diffuse, infiltrating tumor which involves surrounding structures, more especially the liver, and in the liver may metastasize widely. Depending upon the position of the tumor and the secondary fibrosis, the gall bladder may be distended or very markedly shrunken. Histologically, the tumor is usually a cylindrical cell carcinoma of the simplex type, but adenocarcinoma and mucinous carcinoma occur. More rarely the tumor proves to be a squamous epithelioma. This is probably due either to metaplasia of epithelium in a chronically inflamed gall bladder, or in some instances is obviously due to metaplasia after the tumor has been established. Although primary carcinoma is described in the larger ducts, where it occurs especially at the junction of ducts, such as the junction of the cystic and hepatic ducts, the commonest situation is at the opening of the common duct into the duodenum. It is usually a limited growth but may metastasize



FIG. 311—Multiple papillomata of gall bladder.

widely. As a rule there is stenosis of the common duct, sometimes with stenosis of the pancreatic duct and secondary atrophy of the pancreas. As has been mentioned when discussing tumors of the liver, the tubular variety of primary carcinoma of the liver is presumed to originate from intrahepatic bile ducts. Secondary tumors of the gall bladder and of the extrahepatic bile ducts usually invade by direct extension from other situations, but rarely true metastases may be encountered. For more extensive discussions of these conditions the reader is referred to the work of Warthin, of Ewing and of Konjetzny.

PANCREAS

Congenital Anomalies.—Absence of the pancreas is confined to severe monster formation. The head of the pancreas may be large, may partly or completely encircle the duodenum, or may be almost completely separated from the tail by a small midportion. Accessory pancreas, usually multiple, may be found in jejunum, duodenum, stomach, mesentery and other situations. Accessory spleens may be found in the tail of the pancreas. Transposition occurs in situs viscerum inversus. The duct may be double (persistence of duct of Santorini) and may enter the duodenum or even the stomach independently of the common bile duct. Obliteration of the pancreatic duct may accompany congenital obliteration of the bile ducts (Hess).

Retrogressive Changes.—The most important pigmentation is that in hemochromatosis. This has been discussed in the chapter on pigmentations. The lesion is usually associated with that type of diabetes known as “diabète bronze.” The pigments, hemosiderin and hemofuscin, are found in the connective tissue, which is usually increased in amount (fibrosis) and also in cells of the acini and the islets (Sprunt). The organ may be grossly brown in color and is usually firm. Cloudy swelling and fatty degeneration occur under the usual circumstances such as infectious diseases and various kinds of poisoning. Fat infiltration is often referred to as lipomatosis of the pancreas. It occurs especially in obesity. The fat is found in the interlobular connective tissue, and there is commonly associated a variable degree of atrophy of the parenchyma. In extreme cases the organ is a fatty mass with little pancreatic substance visible. Amyloid occurs in the smaller vessels and sometimes in the islets, in cases of extensive amyloidosis.

Fat necrosis is more truly a fat tissue necrosis involving the cytoplasm and nucleus as well as the fat, and has been discussed in the chapter on necrosis. It occurs in acute pancreatitis, in hemorrhage in the pancreas, in obstruction of the ducts, especially by gall stones, following trauma of the pancreas and any condition which destroys pancreatic tissue and liberates the ferments. Rare cases are found without identified cause. It affects the fat of the pancreas, omentum, mesentery, abdominal wall and may rarely occur more remotely, as in the liver and subcutaneous fat. The areas rarely exceed a few millimeters in diameter and appear as well defined, firm, yellow or gray, dry soapy nodules, sometimes surrounded by small areas of hyperemia. The necrosis is apparently due to liberation from the pancreas of lipase and trypsin, the latter

destroying cellular tissue and the former splitting the fat. The glycerol is absorbed, the fatty acids remain and combine with alkali to form soap and in part may crystallize. Histologically, there are found necrosis of the parenchyma of the cells, with the various nuclear changes of necrosis. The fat has disappeared or, when soap has formed, the latter is likely to take the basic stain, probably because of the presence of calcium, and appears as a finely granular substance in the oil spaces. If crystallization has occurred, acicular spaces are observed due to solution of the crystals in the process of embedding and staining. There may be reactionary marginal hyperemia, usually with hemorrhage, or there may be reactionary inflammation, sometimes suppurative. The glycerol liberated, the amount of fatty acids formed, the amount of soap

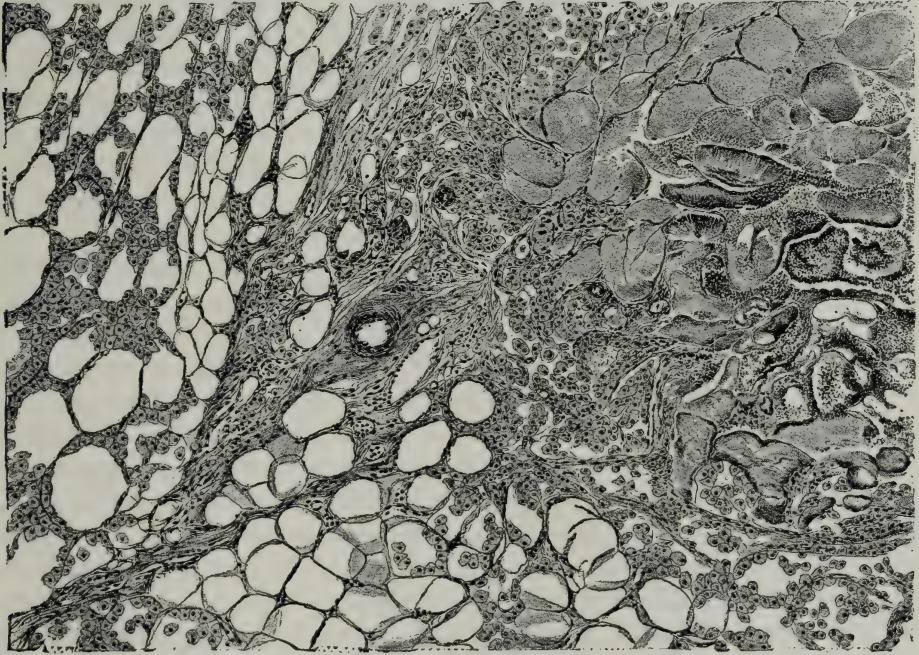


FIG. 312—Fat necrosis.

formed, even though it be slightly soluble, is not sufficient to account for the intoxication which may accompany the condition, so that it is assumed that the causative disease rather than the fat necrosis leads to severe symptoms when they are present.

Circulatory Disturbances.—Passive hyperemia occurs with general passive hyperemia. The pancreas may be large, dark red or purple, and firm. Minute hemorrhages are not infrequent in passive hyperemia and in the hemorrhagic diseases. Large hemorrhages may occur without well defined cause, especially in obese patients, and often give all the signs and symptoms of acute hemorrhagic pancreatitis. This so-called pancreatic apoplexy is usually without known cause. Cases of sudden death sometimes come to autopsy with pancreatic hemorrhage as the only finding of importance. Arteriosclerosis of the

pancreatic vessels is unusual in such instances and cannot be regarded as a cause. It is sometimes difficult to distinguish between pancreatic apoplexy and hemorrhagic infarction of embolic or thrombotic origin.

Acute Inflammations.—The acute inflammations of the pancreas are usually divided into three varieties, acute suppurative, acute hemorrhagic, and acute gangrenous pancreatitis. In some of these the inflammation is so obviously secondary that they are referred to as necroses (see von Linhardt). It must be understood, however, that these lesions are not always distinct and separate, but the name given usually describes the outstanding feature. Acute suppuration of the pancreas may be the result of extension from neighboring suppuration, as for example, suppuration in the lesser peritoneal cavity resulting from gastric ulcer. Similarly, inflammation from other organs in the neighborhood of the pancreas may lead to abscess formation in the pancreas. Conversely, abscess in the pancreas originating from other neighboring foci, or perhaps also from pyemia, may rupture into the greater or lesser peritoneal cavity or into neighboring organs such as the stomach. There are no especial features of abscess in the pancreas other than the fact that they may be complicated by fat necrosis, and not infrequently show a small amount of hemorrhage into the organ.

Acute hemorrhagic pancreatitis occurs most frequently in obese individuals in middle life, and especially those who have had previous gastric disturbances. The symptoms are admirably described and analyzed by Albrecht in her comprehensive view of the subject of diseases of the pancreas. The disease is marked by sudden onset with collapse of the patient, runs a rapid course, and leads to death within a day or two. Upon gross examination, the organ is large, firm and infiltrated with blood. The pancreas and neighboring fatty tissues show more or less extensive fat necrosis. Microscopically, in addition to the diffuse hemorrhage there are found necrosis of the fat, various degrees of cloudy swelling and necrosis of parenchyma, and an exudate of leucocytes and other cells of acute inflammation often enmeshed in fibrin. The capillaries are particularly likely to show fibrin thrombi. The abdominal cavity contains a serous exudate sometimes distinctly hemorrhagic. This was at first thought to be largely responsible for toxic manifestations of the disease, but Whipple has found that in experimental animals this material is not poisonous. Many hypotheses have been advanced as to the cause of acute hemorrhagic pancreatitis, but with the exception of that advanced by Opie none is definitely tenable. Experimentally, numerous substances have been injected into the pancreatic duct with resultant hemorrhagic pancreatitis, but it is doubtful that with the exception of bile any of these substances would be able to gain access to the duct during life in man. Opie noticed the frequent occurrence of acute hemorrhagic pancreatitis in patients with gall stones, and showed that lodgment of gall stones in the ampulla of Vater could easily provide for the backing up of bile into the pancreatic duct. Cameron and Noble have shown that the possibility of backing up into the pancreatic duct is, according to anatomical structure, possible in the majority of human individuals. Opie

demonstrated that in dogs it is possible to produce acute hemorrhagic pancreatitis by injecting the bile of the same or another animal into the pancreatic duct, either through the duodenum or directly into the duct. Flexner demonstrated that the bile salts are the constituents of bile capable of producing this damage, and suggests that their diffusibility is reduced by the colloid constituents, so that under certain circumstances a limited backflow may be responsible for cases of chronic pancreatitis that also are found to be associated with cholelithiasis. The differentiation between simple hemorrhage in the pancreas and acute hemorrhagic pancreatitis is sometimes attended with difficulty, because of the fact that there may be a reactionary exudation in response to the presence of the hemorrhage. As a rule, however, the inflammatory and destructive phenomena are much more marked in hemorrhagic pancreatitis.

Acute gangrenous pancreatitis, according to Fitz, is the result of acute hemorrhagic pancreatitis in the majority of instances, although it may be primary or it may follow other destructive lesions of the organ. The disease resembles hemorrhagic pancreatitis in most respects save that it is likely to run a much longer course. The pancreas is large, soft and friable and it may be mottled red and gray, or dark brown or black in color. The nearness of the pancreas to the intestinal canal accounts for the gangrene, due to invasion by saprophytic organisms. Large masses or even the entire pancreas may slough away and separate from the neighboring structures. Suppuration of the lesser peritoneal cavity is almost constant in this disease and may extend to the greater peritoneal cavity.

Chronic Inflammations.—As age advances the amount of supporting connective tissue of the pancreas gradually increases, and it is sometimes difficult to distinguish in adult life between minor degrees of chronic pancreatitis and the ordinary increase in connective tissue. As a rule, however, foci of lymphoid and other mononuclear cells, or wide distribution of these cells, indicate the inflammatory nature of the condition. Opie recognizes two varieties of chronic interstitial pancreatitis, namely, the interlobular and the interacinar. In either case the organ is distinctly firmer than normal, and when the connective tissue is interlobular the broad bands of connective tissue separating the parenchyma may be visible in the cut section of the organ. Microscopically, the interlobular forms show definite overgrowth of connective tissue, which separates more distinctly the pancreatic lobules. In this condition, overgrowth of connective tissue separating the acini is not likely to be at all marked. Rarely, the overgrowth of connective tissue may be so definitely distributed about the pancreatic duct as to justify the term "chronic abdominal perisialodochitis." In the interacinar forms the connective tissue growth is principally between the acini separating them, thus rendering them more distinct. Rarely, the connective tissue may extend into the acini and isolate individual cells. This interacinar form of pancreatitis is of particular importance because it is more frequently associated with those changes in the islands of Langerhans, which will be described in connection with diabetes mellitus, than is the interlobular form. The causes of chronic interstitial

pancreatitis include all those causes which may produce fibrosis in various internal viscera, such as chronic poisoning either of internal origin including gout, rheumatism, etc., or of external origin, such as alcohol, lead and other ingested poisons. Of especial importance is the fact that obstruction to the pancreatic duct by calculi, either within the pancreatic duct or in the ampulla of Vater, obstruction by the presence of tumors or chronic inflammatory masses, is followed by atrophy of the parenchymatous substance, sometimes going on to complete disappearance, overgrowth of connective tissue, and persistence of the islands of Langerhans. Certain cases appear to be due to arteriosclerosis but this is not a common cause. Chronic interstitial pancreatitis

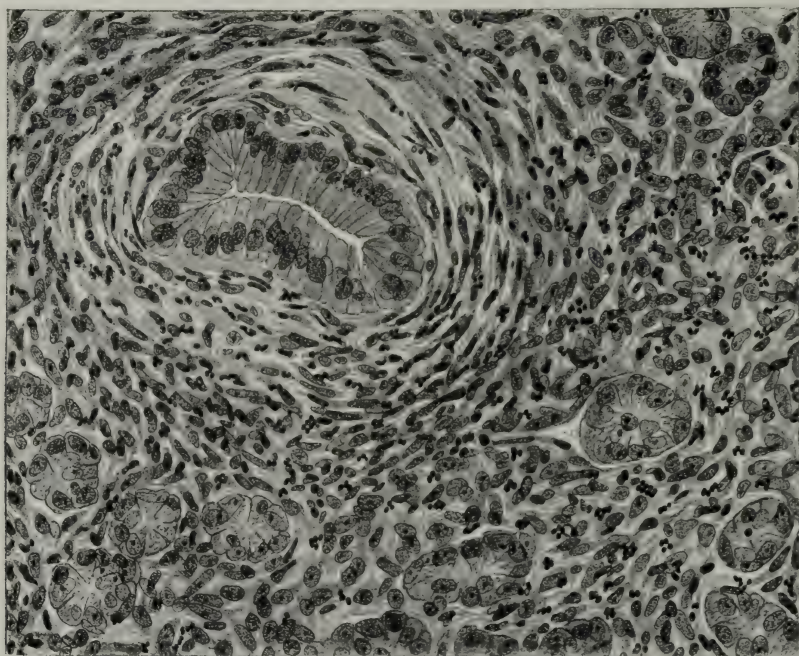


FIG. 313—Chronic interstitial pancreatitis.

is sometimes associated with cirrhosis of the liver and it seems probable that the cause of the latter operates to produce the former. Some cases are entirely obscure as to origin. This appears to be particularly true in those cases which lead to disease of the islets of Langerhans and consequent diabetes mellitus.

Infectious Granulomata.—Tuberculosis rarely affects the pancreas. Even in most advanced cases of generalized miliary tuberculosis the pancreas often escapes, and when miliary tubercles are reported they are usually in the interstitial tissue rather than in the parenchyma. Tuberculous involvement may extend from tuberculosis of neighboring lymph nodes and other organs.

In congenital syphilis the pancreas is often found to be large and firm. Microscopically, it shows what may be signified as a more or less specific form of chronic interstitial pancreatitis. As with other organs in congenital syphilis, the parenchyma is poorly developed and the acini are likely to show

fewer cells than in normally developed organs. The mesoblastic tissue remains in excess and shows greater or lesser differentiation toward the adult type of interstitial connective tissue. Perivascular and adventitial infiltration of lymphoid cells is likely to be prominent. Special stains show large numbers of the spironema pallidum. The relative increase of connective tissue affects the intralobular and interacinar connective tissue, and there may be intra-acinar fibrosis. Acquired syphilis affects the pancreas very frequently, according to the studies of Warthin, and is distributed as an interacinar or interlobular form, often especially marked about the ducts. With precise technic the spironema may be demonstrated. Infiltrations of small and large mononuclear and plasma cells are common and sometimes associated with mucoid connective tissue. The blood vessels show varying degrees of sclerosis and the ducts often show thickening of the walls and dilatation. The parenchyma is atrophic and commonly there is fat infiltration of the connective tissue. The islets of Langerhans may show fibrosis and connective tissue hyalin. In Warthin's 150 cases, six were diabetic. Gumma of the pancreas is rare.

Tumors.—The benign tumors are relatively frequent and include lipoma, myxoma, chondroma and fibroma, the last being sometimes pedunculated. Adenoma of the pancreas may be solid or cystic or exhibit papilliferous cysts. Rare cases of adenoma are thought to originate from the islets of Langerhans (Goldblatt).

Primary carcinoma is the most frequent primary tumor of the pancreas. It is most common in the head of the pancreas, sometimes extends throughout the entire organ and rarely is observed in the tail. Grossly, it is more frequently a scirrhous carcinoma than medullary. It may be a large projecting mass of several centimeters in diameter or may be so small as to be found with difficulty. Microscopically, it is possible to distinguish the carcinoma simplex and the adenocarcinoma. The mucinous type of carcinoma is infrequent. Very rarely the carcinoma may show metaplasia with the formation of squamous epithelial cells. The size and shape of the cells varies in different carcinomas and it is suggested that if the type of cell be of large round form, the origin is from the acinar cells; if the cells be small polyhedral cells with deeply chromatic nuclei, it is supposed that the tumor originates in the islets of Langerhans; if the cells be cylindrical in character it is supposed that the tumor originates in the pancreatic ducts. It must be remembered, however, that in their development, cancer cells may alter their morphology and the determination of derivation purely on the basis of cells found is often fallacious. Metastases occur principally to the regional lymph nodes and in a large percentage of cases to the liver. Occasionally they may be widespread. The presence of the tumor may cause obstruction to the pancreatic duct and resultant fatty stools. Involvement and compression of the common ducts may produce icterus. Tumor thrombi may occur in the portal veins with all the sequences of stagnation of circulation in the portal area. Rarely intestinal obstruction is caused by the carcinoma. Destruction of the pancreas may be so extensive as to produce diabetes mellitus.

The sarcoma is a rare primary tumor in the pancreas and is said to occur most frequently in the head of the organ. It is usually a round cell sarcoma but may be a spindle cell sarcoma or indeed be of other forms.

Secondary tumors in the pancreas are not especially common. Secondary carcinoma sometimes occurs. Of the sarcomata which may be secondary in the pancreas, the melanotic sarcoma is distinctly the most frequent.

Cysts.—There are three forms of true cysts of the pancreas which show a lining of epithelial cells, and in addition a fourth form which is referred to as

pseudocyst or cystoid. Among the true cysts are the so-called proliferation cysts such as occur in adenoma and adenocarcinoma. Rarely there is also observed a congenital cystic disease of the pancreas, apparently due to occlusion or stenosis of the smaller ducts during fetal development of the organ. Retention cysts may involve the larger ducts of the pancreas either in a diffuse general dilatation or a more nodular type of dilatation. This is usually due to calculi in the ducts, to tumor pressure or invasion, or compression by inflammatory masses. Multiple retention cysts are observed occasionally in the smaller ducts, due apparently to fibrosis of the organ leading to compression of the smaller divisions of the duct system. The pseudocysts or cystoids are believed to originate principally from hemorrhage and represent subsequent encystment of a hematoma. These



FIG. 314—Multiple calculi in pancreatic ducts. Note cylindrical dilatation of ducts. Army Medical Museum 16379.

are usually solitary, large, occur in the tail of the pancreas, and project outside the organ, sometimes ultimately becoming more or less separated from it. The contents may be serous, serosanguinous or bloody. The origin may be in hemorrhage such as occurs in the so-called pancreatic apoplexy, or as the result of trauma.

Pancreatic Calculi.—These are probably entirely the result of inflammatory disease in the duct, since experimental ligation of the duct does not lead to their formation. As with the salivary glands, calculi are usually made up of calcium phosphate or in some instances of calcium carbonate, and in the

pancreas there is usually a mixture of other salts. The calculi may be single or multiple and often attain considerable size. They are granular on the outer surface, pale yellow or grayish-white in color, soft and easily broken up. They may lead to obstruction of the duct, with consequent atrophy of the parenchymatous substance, other than the islets of Langerhans, and considerable fibrosis. There may be moderate or cystic dilatation of the larger ducts, usually associated with a chronic catarrh. Occasionally fat necrosis takes place. In some instances secondary infection occurs and suppuration ensues.

Foreign Bodies and Parasites.—The most important foreign body is the gall stone. This, situated in the pancreatic duct, may show additional deposits of calcium salts, and depending upon the degree of obstruction, leads to the sequences enumerated above under pancreatic calculi. The animal parasites include the echinococcus cyst, occasionally ascarides and rarely some of the forms of distoma.

The Relation of the Pancreas to Diabetes Mellitus.—Although glycosuria with variable degrees of hyperglycemia may be produced experimentally by the injection into animals of epinephrin, phloridzin and other agents, depression of respiration by morphine, stimulation of the splanchnic nerves, and puncture of the floor of the fourth ventricle, the resultant alteration of carbohydrate metabolism is only temporary. The only experimental condition truly comparable with human diabetes is that produced by total extirpation of the pancreas, as shown by Minkowski and von Mering. It is now known that absolutely complete extirpation is not necessary, and Allen has shown that survival of one-eighth of the gland is sufficient to prevent diabetes. Various studies have focussed attention upon the islets of Langerhans as being directly concerned with carbohydrate metabolism. Opie found that in his human cases there was fibrosis of the islets and in several instances hyalinization of the cells of the islets. Weichselbaum and Stangl found the same changes and drew attention to hydropic vacuolization of islet cells as of considerable importance. Nevertheless, such changes may occur in patients without diabetes and many pathologists have the same experience as Major, who, with the usual technique and autopsy material, was unable to demonstrate islet lesions in 54 per cent. of his diabetics. As emphasized by Bensley and by Graham, in important studies and reviews, promptness of fixation and great care with staining technique are necessary to demonstrate finer lesions. With due attention to these details, Allen claims to be able to make correct diagnoses on the basis of the anatomical material in nearly 100 per cent. of instances. Aside from the coarser changes described, proper technique will show disappearance of granules, hydropic vacuolization and even fragmentation, of the beta cells of the islets (see Bowie). Postmortem changes progress so rapidly in the pancreas as to necessitate almost immediate fixation for accurate studies. Physiological, clinical and morbid anatomical facts point conclusively to the islets as of essential importance. Occlusion of the pancreatic duct by lesions in man, and experimentally in animals, may lead to extensive or complete atrophy of the parenchyma with preservation of islets and no diabetes.

Tumors and acute destructive lesions of the pancreas must destroy practically the entire gland before diabetes ensues. The work of Macleod, Banting, Best, Collip and others has shown that an extract of islets, insulin, will restore carbohydrate metabolism in depancreatized animals and in diabetic human patients.

The lesions in the islets may vary markedly in the same pancreas and a considerable number may be normal. In the cases studied by Warren and Root, glycogen infiltration of the cells of Henle's loops in the kidneys, ordinarily common, is often absent in insulin treated cases. There is likely to be fibrosis of myocardium, arteriosclerosis and vascular disease of the kidneys. The vascular lesions probably are the important feature in causing infarction of extremities (gangrene) frequent in diabetics, especially those who are obese.

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CHAPTER XVIII

THE URINARY SYSTEM

KIDNEYS.
RENAL PELVIS AND URETER.
URINARY BLADDER.
URETHRA

THE KIDNEYS

Congenital Anomalies.—Bilateral agenesis or aplasia of the kidneys is rare, is incompatible with life and may be associated with reduced amount of amniotic fluid. Unilateral aplasia is not uncommon, occurs more frequently in males and on the left side (Huffman). The other kidney usually undergoes hypertrophy so as to equal in weight that of the two kidneys, which in the adult is about 300 grams. Unilateral congenital hypoplasia is much more rare than aplasia.

The fused or horseshoe kidney is unusual but not rare, being found according to Keyes in thirty cases in 21,218 autopsies. The lower poles of the two kidneys are connected either by an isthmus of kidney substance or by a connective tissue band. Fusion at other parts is extremely rare. The renal pelves may be fused, or separate, or may be anomalous. The ureters pass anterior to the isthmus and they, as well as the arteries, may be anomalous.

Nephroptosis, or floating or movable kidney, is an acquired downward displacement of the organ which is more common in women, especially those of advanced years, and affects the right more often than the left kidney. Although it may occasionally be congenital, it occurs usually in connection with general ptosis of the abdominal viscera such as may be observed in old age due to wasting of the belly fat, or as a sequel of pregnancy. Downward displacement of the liver from tight lacing or the weight of tumors, atrophy of fat in wasting diseases, and even trauma, may cause nephroptosis. The kidney is in a lower and more horizontal position than normal; in extreme cases it may move downward and forward to the iliac fossa. Kinking of the ureter may produce hydronephrosis, a distention of the renal pelvis with subsequent atrophy and fibrosis of the kidney. In rare cases the organ may undergo necrosis as a result of torsion of the blood vessels.

Dystopia, congenital misplacement of the kidney, indicates an anomaly dependent upon a failure of the kidney to ascend to the normal position. The kidney may therefore be found in the lower abdomen or pelvis. This anomaly usually affects the left kidney but may affect both. Such a position of the kidney may lead to erroneous clinical diagnoses of tumor or inflammatory mass. More or less complex anomalies of arteries and veins and malformations of parts of the genital tract are frequently associated with dystopia of the kidney (Huffman).

Fetal lobulation of the kidneys is a persistence in adult life of the fetal

lobes and is so common as to be regarded as normal. Frequently in adult life the two poles of the kidneys are found to be separated by an ingrowth of cortex, often with more or less complete division of the renal pelvis into two parts. Accessory kidneys are rare.

The congenital anomalies of the types mentioned are usually ascribed to misplacement or other alteration of the renal buds (Pohlman, Huntington). The congenital cystic kidney, in all probability of embryonal origin, will be considered with cysts.

Pigmentation and Mineral Deposits.—The deposition of hemosiderin in the kidney is uncommon and perhaps occurs more often as the result of perni-

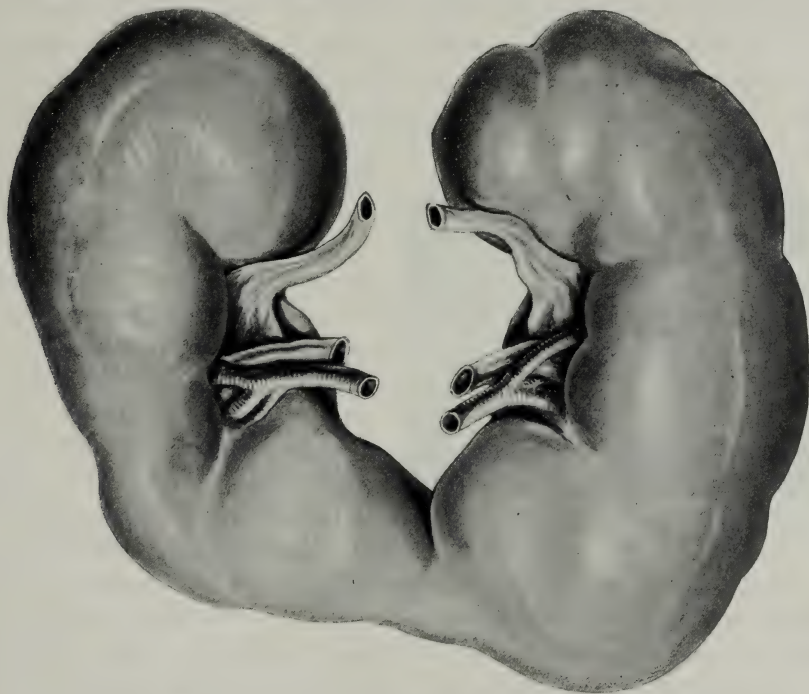


FIG. 315—Horseshoe kidney, showing relation of blood vessels and ureters.

cious anemia than of prolonged passive hyperemia. The iron-bearing pigment is found in the cells of the convoluted tubules and sometimes in other parts of the tubules. Rarely it is found in the interstitial connective tissue. Hemoglobinemia, after passing the threshold of excretion by the kidney, leads to hemoglobinuria. This occurs especially in the so-called blackwater fever of malaria, poisoning by potassium chlorate, extensive burns of the body surface, is occasionally observed in the course of pregnancy and may result from prolonged muscular exercise as in long marches. The cortex and peripheral parts of the medulla are of a dark brown color. Much the same color is observed in cases of methemoglobinemia and methemoglobinuria. In cases of icterus of any origin the kidney may be deeply pigmented. In infants bilirubin may be deposited as needle-like crystals or rhomboid plates in the lumina of the tubules, or sometimes in the epithelium and even in the connective tissue.

In the icterus of adults, bilirubin is most often observed as a pigmentation of casts in the tubules, but where there is necrosis of the epithelium it may also be deeply pigmented. The pigment of ochronosis may be found in convoluted tubules and glomeruli and may stain casts.

In young infants, deposit of salts of uric acid occurs in the form of so-called uric acid infarcts and in adults in association with gout. It is supposed that the changes in metabolism incident to birth, so alter protein catabolism in infants as to produce an excess of urates. The naked eye examination of the kidney shows crystalline yellow streaks arranged radially in the tips of the pyramids, often accompanied by a deposit of uratic sand in the pelvis. Microscopically, there are small crystalline masses and spheroliths in the tubules and occasionally also in the connective tissue. In gout the kidney sometimes shows fairly large masses of chalky material in the pyramids. As a rule such patients also exhibit chronic renal disease. Microscopically, the urates are present in the form of needle-like crystals and rhomboid plates in a mass of

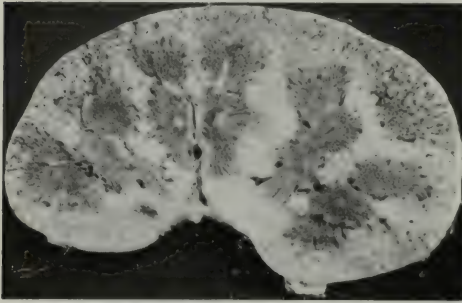


FIG. 316—Advanced cloudy swelling of kidney.
Army Medical Museum, No. 13331.

necrotic tissue and surrounded by an overgrowth of connective tissue. In old people, especially those with atrophic kidneys and those the victims of chronic renal disease, it is not uncommon to find *calcium deposits* in the tips of the pyramids, sometimes associated with a certain amount of fat deposit. Microscopically, there is a granular mass about the walls of the tubules, sometimes also in the interstitial connective tissue. In the so-called calcium metastasis the kidney may show deposits of calcium salts in the walls of the renal arteries, sometimes in the connective tissue of the cortex and not rarely in the loops of the glomeruli. In the late stages of mercuric chloride poisoning the necrotic epithelium becomes infiltrated or encrusted with calcium salts. In argyria the silver salts are found as minute black granules in the membrana propria of the glomerular loops which, according to Ohmori, attracts the silver from the blood.

Retrogressive Changes.—Cloudy swelling, fatty degeneration and amyloidosis are of especial significance because they may produce signs and symptoms similar to those of Bright's disease. In the discussion of that topic these lesions will be grouped under the general heading of nephrosis. Cloudy swelling of the kidneys occurs in all those conditions described in discussing the general pathology of cloudy swelling, including particularly the acute infectious diseases, passive hyperemia, profound anemias and various forms of poisoning. The kidney is soft, swollen, increased in weight, but as a rule does not attain the size and weight observed in acute nephritis. The capsule strips readily, the organ cuts with normal resistance and shows a thick bulging, pallid, "parboiled" cortical substance in which the glomeruli are usually visible as

small red points. The lighter cortical striations are wider than are the darker. The change affects the cells of the convoluted tubules more strikingly than others, as is shown microscopically by the increase in size and increased granularity of the cells. The increase in size may lead to almost complete obliteration of the tubular lumina, but in the later stages the parts of the cell next to the lumen apparently drop away and the thickness of the cell ultimately is reduced. Where the lumen is open there is usually a deposit of albuminous granular material. In uncomplicated cloudy swelling the glomeruli are normal. In cases where there is excessive imbibition of water, the microscopic picture is that of hydropic infiltration with large droplets in the tubular cells. The tubular epithelium may show also hyaline droplets. It seems at least possible that the milder renal disturbances, such as albuminuria, oliguria and cylindruria, occurring in acute infectious diseases are due to cloudy swelling, a condition found almost constantly at autopsy in such cases. Wilcox and Little find that children with acute infectious diseases often show slight accumulation of uric acid in the blood, and less commonly accumulation of total non-protein nitrogen and creatinin, an indication of depression of renal function which we assume to be due probably to minor degrees of cloudy swelling.

Fatty degeneration occurs under much the same conditions as cloudy swelling, except that the causes persist longer or operate with greater intensity. It is especially likely to be prominent in severe anemias and also constitutes an integral part of certain forms of chronic nephritis. Fatty degeneration is also found in diabetes, exophthalmic goitre, in pregnancy, if complicated by eclampsia or nephritis, in poisoning by fungi, by phosphorus and other agents. The condition in itself has no particular influence upon the size of the kidney, but may be the cause of considerable reduction of consistence. Grossly, there may be irregularly defined patches of yellow several millimeters in diameter on the outer surface, but as a rule this change is more prominent in the cut surface, especially in the interpyramidal cortical substance. Less commonly the entire cortex is of a diffuse yellow color. Demonstrated by special methods, the fat appears in the early stages as small globules within the cell near the basement membrane, and in later stages may involve the entire cell. The epithelium of the loops of Henle and the distal convoluted tubules may contain fat normally (Fischer, Prym), but fat in the proximal convoluted tubules always means pathological alteration. This is usually neutral fat. In diabetes the fatty substance is, according to Aschoff, a cholesterol-glycerol-ester mixture. Epithelial degeneration is also accompanied (Stoerck, Adami) by a deposit of lipid droplets of protagon or myelin. Most investigators believe that severe fatty change reduces the functional capacity of the kidney, a view with which Fahr disagrees. Fatty degeneration of the glomeruli is common in certain forms of chronic renal disease, especially in the terminal stage of chronic glomerulonephritis.

The deposit of microscopically demonstrable glycogen occurs practically only in connection with diabetes mellitus. With the special stains it is seen

as large or small droplets, situated particularly in the ascending limb of the loop of Henle. In the ordinary preparation the glycogen is dissolved out and these cells are markedly vacuolated.

Hyalin occurs in various chronic diseases of the kidney and in the atrophy of old age, affecting particularly the interstitial connective tissue, the blood vessel walls, the capsule of the glomeruli, and the capillaries of the loops. Hyalin in the form of droplets may also be observed in the capillary loops in connection with acute infectious diseases, more especially diphtheria, and in

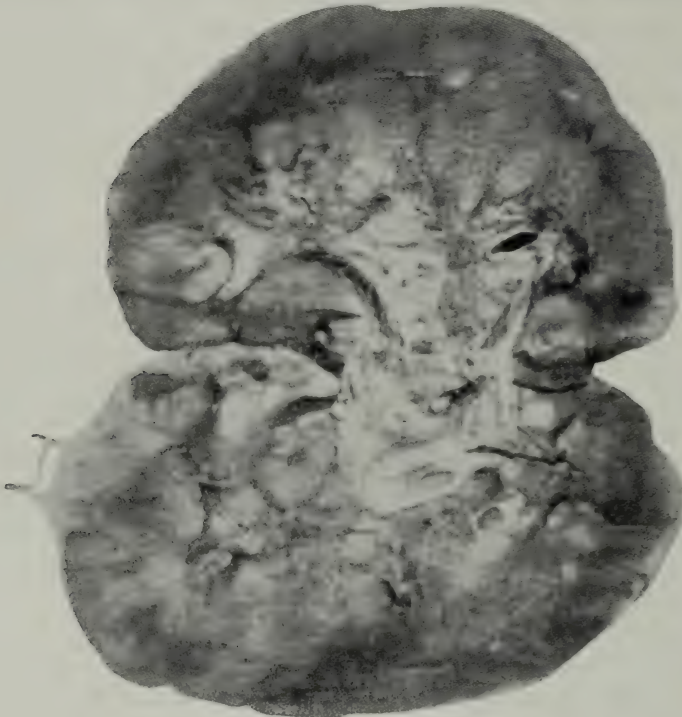


FIG. 317.—Cut section of kidney stained by Lugol's solution and sulphuric acid to show amyloid. The darkly stained glomeruli are seen best in the interpyramidal cortex.

experimental uranyl nitrate poisoning. Epithelial hyalin has been referred to above.

Amyloidosis of the kidneys is important clinically and pathologically. It is usually associated with amyloid in the liver and spleen. As a rule, the organ is large, pale and firm, constituting one of the forms of large white kidney. The capsule strips with slight difficulty leaving a smooth surface. The organ cuts with increased resistance, and shows a pallid, thick cortex and a somewhat fibrosed pyramid. With Lugol's solution and dilute sulphuric acid the diseased glomeruli appear as bluish-black points in the cortex. The use of special stains microscopically shows the amyloid deposited in the capillaries of the loops of the glomerulus, more especially near the entrance and exit of the vessels. It is also observed in the arteriæ rectæ and interlobular arteries.

In advanced cases it may be found occupying the position of the basement membrane between the cells of the tubules and the supporting connective tissue. With the common stains the position of the amyloid in the glomeruli is sufficient for a presumptive diagnosis, but these stains do not show it well in the other situations. The studies of Obmori indicate that amyloid is first deposited just inside the membrana propria of the glomerular loops and subsequently involves the membrana which then disappears in the amyloid mass.

Atrophy of the kidney is usually accompanied by a greater or less degree of fibrosis. It occurs in old age and in chronic wasting diseases. Occlusion of the ureter leads to wide distension of the pelvis and kidney and after a certain period of time there is marked atrophy of the parenchymatous part with substitution overgrowth of connective tissue (Kitani). Focal forms of atrophy are particularly common when the renal arteries are the seat of arteriosclerosis, in which condition irregularly disposed conical areas of renal substance undergo atrophy with connective tissue growth and shrinkage. This will be referred to again. In all these instances the glomeruli resist the atrophic change for a considerable period, but when the connective tissue growth is well established, fibrosis is likely to affect the capsule and glomerular loops of the Malpighian bodies and leads ultimately to their conversion into small fibrous balls.

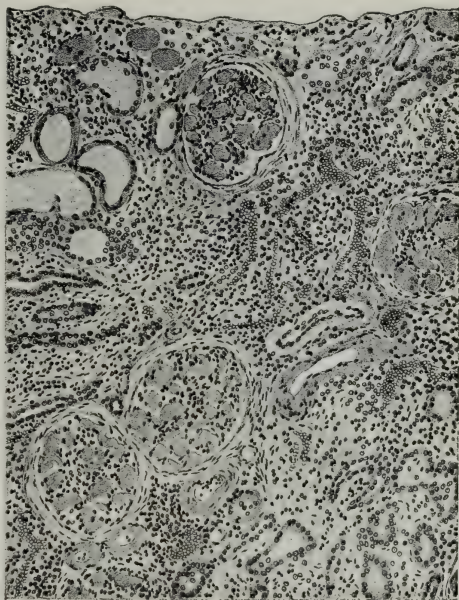


FIG. 318.—Amyloid in the loops of the glomerular tufts and in the walls of small arteries.

Circulatory Disturbances.—Active hyperemia is observed more especially in the various types of acute inflammation of the kidney, and may be seen when, for various reasons, such as excision of the opposite kidney, the organ is called upon to perform extra work. Passive hyperemia is of the utmost significance both clinically and pathologically. At postmortems, variable degrees of hyperemia are observed as a result of death from almost any cause, and the condition becomes more prominent by the settling of blood back into the kidneys. The most important cause of prolonged passive hyperemia is disease of the heart. It also occurs in chronic diseases of the lungs and pleura. Involvement of the renal veins or the inferior vena cava by tumors or thrombosis, pressure by tumors and inflammatory swelling, and probably also the accumulation of large quantities of fluid in the peritoneal cavity such as occurs in the ascites of hepatic cirrhosis, may cause passive hyperemia of the kidneys. In the earlier stages the kidney is large, dark red in color, with a tense capsule

which strips with ease. The outer surface is smooth and moderately firm. The organ cuts with normal resistance and shows a moderate thickening of the entire substance and in the cut surface is dark red and bleeds freely. The color of the pyramids is purple in contrast to the dark red of the cortex. The glomeruli may be seen as prominent dark red points. The stellate veins of the outer surface as well as those of the pelvis are usually prominent. As time goes on, interstitial connective tissue increases in amount and the kidney is reduced in size and increased in consistence, usually smooth, however, and only rarely granular on the outer surface. The greater the amount of connective tissue the more adherent is the capsule and the more resistant is the organ to cutting by the knife. Correspondingly, as the fibrous overgrowth continues, the cortex is reduced in thickness and the pyramids are likely to show the gray color of fibrosis near their tips. The glomeruli continue to be visible grossly as red points. Microscopically, practically all the vessels of the kidney are distended with blood, more especially those of the venous circulation. The glomerular tufts are filled with blood and may occupy the entire capsular space. The tubular epithelium is the seat of cloudy swelling and in the tubular lumina, also in the subcapsular space where it is patent, there is granular albuminous precipitate. Small interstitial hemorrhages are sometimes observed and red blood corpuscles may be seen within the tubular lumina. Although hyaline and granular casts may be found in the urine, it is unusual to observe them in the kidney section. In later stages, connective tissue overgrowth is diffuse throughout the kidney and only rarely shows fairly wide bands at right angles to the outer surface. At this stage the capsule of Bowman and occasionally the tuft may show fibrosis. As has been mentioned above, hemosiderosis is not common in passive hyperemia.

Clinically, the urine is often reduced in amount and of high specific gravity, presumably due to slowing and reduced pressure of the blood current through the glomeruli. There may be considerable amounts of albumin, frequently hyaline and sometimes granular casts, and also red blood corpuscles. Functionally, there is no important accumulation in the body of products of protein metabolism, and as a rule, the dyes used for testing, such as phenolsulphonephthalein, pass through the kidney readily.

Edema is observed in the kidney in the course of inflammations but is apparently more prominent when the glomeruli are seriously injured. It may also be seen in cases of suppression of urine.

Embolism is frequent from thrombi in the arterial circuit, especially thrombi upon heart valves and on sclerotic patches in the aorta and arteries. Lodging in branches of the renal artery, these lead to infarction, which will be discussed subsequently. In fat embolism it is common for globules of fat to pass through the capillaries of the lung and gain access to the kidney where they are most frequently found in the glomerular capillaries. Clumps of bacteria may also lodge in the glomerular loops. Cells from the placenta and also bone marrow giant cells are occasionally embolic in the capillaries of the kidney.

Infarction.—This is most commonly secondary to acute or subacute endo-

carditis, but may also be secondary to thrombosis in the chambers of the heart and to thrombi upon the ulcers of arteriosclerosis. Probably owing to the fact that the left renal artery comes off the aorta less at a right angle than the right artery, the left kidney is somewhat more commonly affected by infarcts than is the right. Our experimental studies, supported by subsequent extensive examination of human kidneys, demonstrates that the earliest infarct is a hemorrhagic infarct. Occlusion of the renal artery leads first to a conical area of hyperemia, purple in color, sometimes surrounded by a narrow zone of compression anemia. The area rapidly becomes hemorrhagic, particularly in the center, and at the end of about forty-eight hours necrosis with decolorization begins. The red infarct is slightly swollen, conical in form, deep red in color and relatively dry in the cut surface. Microscopically, there is cloudy swelling in the early stages, then fatty degeneration and finally necrosis of the tubular epithelium. There is marked hyperemia, conglutination of the red corpuscles, and slight hemorrhage into the interstitial substance, the glomerular spaces and the tubular lumina. Owing to the fact that decolorization appears early in the kidney, the white or anemic infarct is far more common than is the red infarct. In the earlier stages the white infarct is distinctly swollen, bulges upon the outer surface, is pale yellow in color, soft in consistence, friable and surrounded by a narrow zone of reactive hyperemia. The cut surface is irregularly triangular in shape, extending through cortex and sometimes involving medulla, soft, relatively dry and friable in the cut surface. Microscopically, in the early stages there is cloudy swelling, and in the later stages necrosis of the tubular epithelium. The architecture of the kidney is preserved and the blood in the glomerular loops is more or less conglutinated. Later, the cells of the glomerular tufts and of the interstitial connective tissue show nuclear degeneration and solution and finally complete disappearance of the fibrillar substance. The margins show reactive hyperemia, infiltration of large and small mononuclear cells and leucocytes, small globules of fat, apparently transported from the necrotic central part, and sometimes small amounts of blood pigment. Essentially the same changes occur in the kidney substance when the entire renal artery is occluded. The presence of passive hyperemia has apparently no effect upon the course of the infarct. In still later stages the necrotic area is reduced in size and surrounded by a zone of organization and then of cicatrization. If the infarct be small it may become completely cicatrized, but it is only rarely that small areas of necrosis are not visible in the center of the healed infarct. The shrinkage of the conical area of fibrosis, with central necrotic mass of varying size, produces an irregular retraction of the outer surface of the organ, which may involve the entire thickness of the cortex and sometimes the medulla. Clinically, the infarct is of



FIG. 319—A kidney, the seat of numerous healed infarcts and fetal lobulation.

little significance except that occasionally patients may complain of pain in the lumbar region and exhibit a small amount of blood in the urine. It is only when a large amount of kidney substance is destroyed by infarction that there is any accumulation of nitrogenous products or interference with the output of test dyes.

Hemorrhage.—Hemorrhage into the kidney may give no sign clinically, but if there be extension into the surrounding tissue there may be general symptoms and signs of severe hemorrhage. One of the causes of blood in the urine is renal hemorrhage. Hemorrhage occurring into the kidney itself may be due to active or passive hyperemia, to the presence of malignant tumors, to infarction, to inflammations of various kinds, to specific inflammations, particularly tuberculosis, and to direct or indirect trauma. Hemorrhage into the perirenal tissue may be extensive and is usually due to trauma, but occasional cases are observed in which no cause can be discovered. Such a perirenal hematoma may be entirely absorbed. In other cases a capsule of fibrous tissue may form and the sac so constituted may contain a considerable amount of fluid.

Of much clinical importance is the so-called idiopathic or essential hematuria (bloody urine). Cystoscopic examination sometimes shows that the blood comes from only one kidney. If a kidney be excised or the patient come to autopsy, nothing may be found in the kidney to explain the hematuria, although minor degrees of acute inflammation or simple cloudy swelling are commonly encountered. Aschoff is of the opinion that many of these cases are to be explained as due to a transient acute inflammation of the kidney or of the pelvis, which disappears by the time the examination is made. On the other hand, Payne and MacNider find patchy or diffuse fibrosis in such kidneys, and suggest that the hemorrhage is due to rupture of a glomerular vessel and is kept up by the commonly associated high blood pressure. Keyes includes under essential hematuria that due to a variety of definite causes such as hemophilia, scurvy, purpura, poisoning by drugs such as turpentine and cantharides, parasites, especially the distoma hematobium, acute infectious diseases, hydronephrosis, movable kidney, calculi, chronic nephritis, inflammation of the renal papillæ, and the so-called angioneurosis.

Arteriosclerosis.—In the classification of Bright's disease, to be given subsequently, arteriosclerosis of the kidney will be referred to as nephrosclerosis. It is true that arteriosclerosis may affect larger renal vessels without apparent damage to the kidneys. Of much greater importance are those lesions of the kidney which are due to arteriosclerosis, involving on the one hand medium sized arteries and on the other hand small arteries and arterioles. We, therefore, refer to the one as of the arterial variety, formerly called arteriosclerotic nephrosis or primarily arteriosclerotic chronic interstitial nephritis, and to the other as the arteriolar variety constituting one of the forms of the condition formerly spoken of as chronic interstitial nephritis. The arterial form is common in late middle and advanced life, and is spoken of by some as benign because it produces no important functional lesion. The arteriolar

variety almost constantly is associated with arterial hypertension and in its terminal phases may exhibit renal insufficiency. The latter condition is essentially the combination form of Volhard and Fahr, but it is doubtful that it represents more than a nephrosclerosis with a superimposed acute nephrosis or nephritis. Morphologically, it is easily confused with the terminal stage of chronic glomerulonephritis. The associated hypertension is probably the result of arteriolar disease throughout a large part of the arteriolar bed, the diffuse hyperplastic sclerosis discussed in the chapter on cardiovascular system, than to disease of the kidney alone. We shall discuss first the arterial variety of arteriosclerotic nephrosis.

Arteriosclerosis of the medium sized renal vessels does not involve all vessels equally. In a variable number of vessels, the lumen is gradually reduced in size and finally practically occluded. This gradual reduction of blood supply to the given part of the kidney results in atrophy of the parenchyma, either as the result of faulty nutrition, inactivity, or both, and substitution by connective tissue. The latter contracts and the outer surface of the kidney shows irregularly stellate areas of retraction, varying from a few millimeters to a centimeter or more in diameter, in the base of which the organ is firm and gray due to the fibrosis. In cut section the triangular areas of fibrosis below the surface depressions may extend entirely through the cortex and sometimes into the medulla. The visible arteries are usually the seat of considerable sclerosis. The larger vessels, however, may be distinctly sclerotic without producing arteriosclerotic nephrosis. A more or less general fibrosis of the organ may accompany the arteriosclerotic lesion. Microscopically, the atrophic areas show very definite atrophy of the tubules and their cells, sometimes with complete disappearance. The intervening connective tissue is fibrous, sometimes moderately infiltrated with lymphoid cells. The glomeruli show variable changes. The areas less markedly involved show fibrosis of the capsule of Bowman, moderate in extent. There may be slight fibrosis of the tufts, but more characteristic is a certain degree of lobulation of the tufts with minor thickening of the walls of the individual capillaries. Subsequently, the fibrosis of both capsule and tufts becomes more marked and ultimately the glomerulus may be converted into a small ball of fibrous tissue. The medium sized and smaller arteries show extensive endarteritis deformans or obliterans. Occasionally the microscope shows dilatation of some of the tubules within the atrophic area, and these may become so distended as to be apparent grossly as retention cysts.

The arteriolar variety of arteriosclerotic nephrosis, the primarily contracted kidney, the hypertensive arteriosclerotic kidney, is distinctly different in appearance. The degree of reduction in size varies with the duration and intensity of the disease, but is usually slight or moderate. Unusual cases show marked reduction in size and weight. The consistency is also variable in accord with the progress of fibrosis. The outer surface is red or pallid, and instead of being coarsely and irregularly nodular as in the benign form, is more finely and uniformly granular. Small nodules of parenchymatous sub-

stance, 2 or 3 mm. in diameter, project between a reddish-gray network of retracted connective tissue overgrowth. The kidney cuts with increased resistance and shows a narrow retracting cut surface in which the cortex is reduced

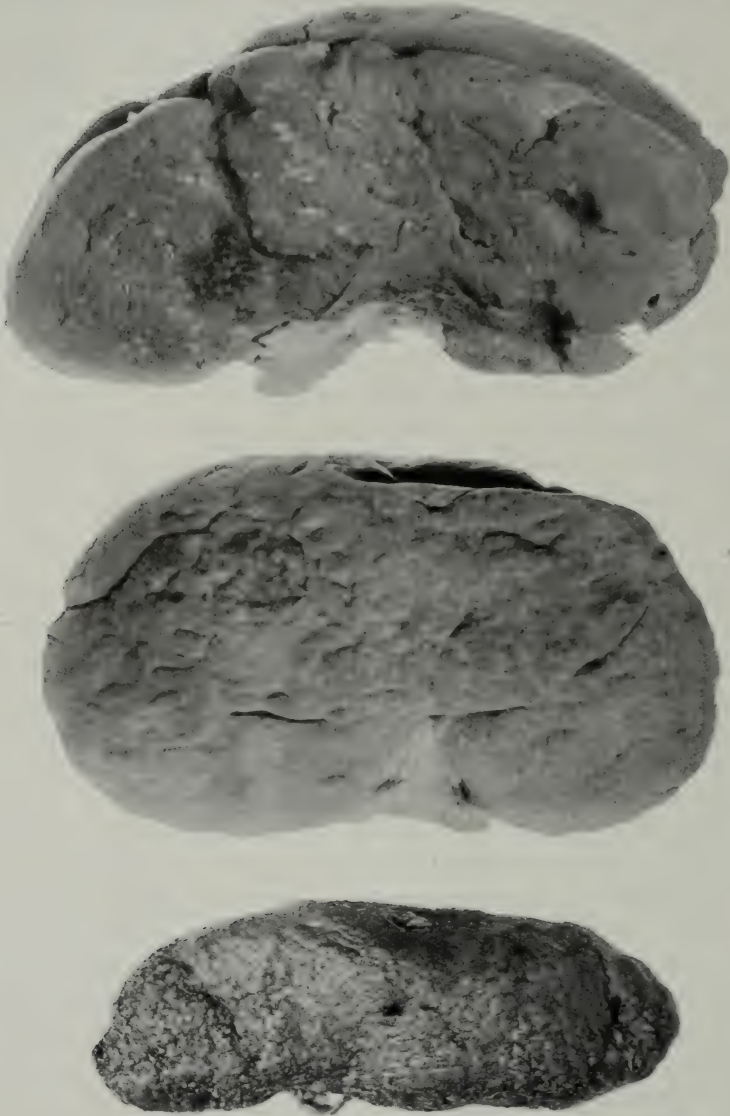


FIG. 320—Varieties of arteriosclerotic kidney. Above is a kidney of about normal size with coarse areas of atrophy and fibrosis. Next is a kidney of about normal size with somewhat smaller areas of retraction. Below is a kidney with innumerable minute areas of retraction, the so-called small red granular kidney or genuine contracted kidney (uniform reduction).

in thickness, the striae irregular and broken up, the pyramids reduced in thickness with their tips pale and fibrous. The pelvis is normal and between pelvis and kidney substance there is an increase in amount of peripelvic fat. The visible renal vessels may or may not be arteriosclerotic. Microscopically, the

fibrosis appears in more or less parallel bands in the cortex, at right angles to the surface. In these bands there is atrophy of the tubular epithelium and of the tubules. The glomeruli show much the same changes as those described in the arterial nephrosclerosis, except that fibrosis is more prominent and lobulation of the tufts not so frequently observed. Lymphoid infiltration into the overgrown interstitial connective tissue is usually more prominent than in the benign arteriosclerotic nephrosis. Vascular sclerosis affects smaller vessels than in the other condition, including the interlobular arteries and arterioles and the afferent arterioles of the glomerulus. The tubules, more especially those in the slightly fibrosed tissue between the areas of denser fibrosis, may show distention, and grossly visible retention cysts are common. They may occasionally attain a diameter of several centimeters and regardless of size are thin walled, show a smooth lining and contain a clear, limpid fluid of low specific gravity. Sometimes the fluid may become inspissated to constitute a hyaline mass. Hyaline and finely granular casts are observed more frequently in the tubules in this disease than in the arterial type of arteriosclerotic nephrosis. Acute degenerative or inflammatory disease may be superimposed upon the primary disease here described.

Anatomically these forms have been sharply distinguished, but arteriosclerosis is not confined strictly to one or other size of artery and consequently various combinations of the two forms are not infrequent. For more adequate discussion the reader is referred to articles and monographs of Ophüls, Oertel, Bell and Hartzell, Jores, Löhlein, Gaskell, Fahr, Volhard and Fahr, and Evans.

In our opinion, it is not possible accurately to correlate degrees of anatomical and functional change, although in many instances there is a rough parallel. In the so-called benign form, systemic blood pressure is essentially normal for the age of the individual, urinary flow is normal or only slightly increased in amount, the urine may be slightly albuminous, there is no important accumulation of nitrogenous wastes in the body and test dyes pass through the organ readily. The most important alteration in the hypertensive or "malignant" form is elevation of systemic blood pressure, both systolic and diastolic being high. Death in such patients is due to intercurrent disease, to heart failure, or to rupture of cerebral arteries rather than to renal insufficiency, and the lesion of the kidney found at autopsy is incidental to the widespread cardiovascular disease rather than primarily responsible for the general condition. This form more often than the "benign" type is accompanied by increased output of urine of low specific gravity, nocturia, slight albuminuria, a few hyaline and finely granular casts, and slight reduction in renal function. The student is advised to study the topic of renal arteriosclerosis in connection with inflammations of the kidney.

Inflammations.—In the case of the kidney, perhaps more than in any other organ, it is necessary to qualify what is meant by inflammations. The suppurative and specific granulomatous inflammations follow the general rules for such lesions. There is also a group of lesions formerly called the non-suppurative inflammations which are included in what is commonly referred to as

Bright's disease. They represent the alterative or parenchymatous type of inflammation. Carefully correlated studies of clinical and pathological manifestations have led to the conclusion that not all of these are truly inflammatory, even according to the rather loose conception of alterative inflammations. Cloudy swelling of the kidneys may, for example, produce many of the clinical signs and symptoms of Bright's disease, but it has long been excluded from that category. Arteriosclerosis may produce severe morphologic lesions in the kidney with little or no functional disturbance, and nephrosclerosis is also sometimes excluded. Chronic passive hyperemia may produce signs and symptoms and exhibit marked anatomical change in the kidney, but it is not usually called a form of Bright's disease. The same is true of hydro-nephrosis and the various exudative inflammations. As a rule the term nephritis refers to the non-suppurative forms; when exudative in character, some

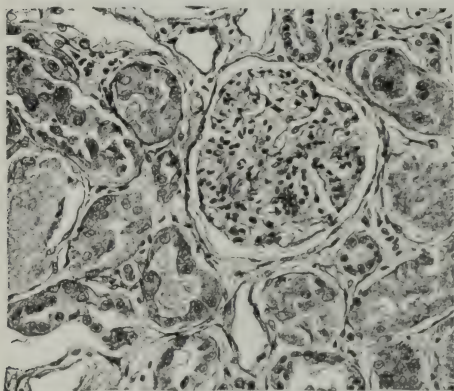


FIG. 321—Necrosis and desquamation of tubular epithelium as the result of poisoning by male fern.

qualifying term is applied as pyonephritis, suppurative nephritis, tuberculous nephritis, etc.

Classifications of this group of renal diseases, as pointed out by Oertel, have been made from five viewpoints, namely etiological, pathogenetic, functional, clinical and morphological. The etiological classifications are unsatisfactory because the causes are often unknown, the pathogenetic because the primary lesion is often obscured by advanced changes, the clinical and functional because of the great diffi-

culty in setting up groups that are sufficiently distinctive, the morphological because of the frequent lack of correlation between anatomical and functional changes. Nevertheless, the morphological classifications are the least objectionable and most widely adopted. There is considerable divergence in terminology of such classifications, but a certain uniformity of idea is fairly well covered by the grouping of Volhard and Fahr into nephrosis, nephritis and nephrosclerosis. This, with certain modifications, will serve as the basis of our discussion. Nephrosclerosis has been considered above.

The term nephrosis is employed here because it has been subjected to less confusing usage than has nephropathy. Included definitely are uncomplicated cloudy swelling, fatty degeneration and tubular necrosis, which have been described in preceding sections. We agree with Bell that those cases which are called chronic nephrosis by Volhard and Fahr should rarely if ever be included. Aschoff, however, regards the kidneys of diabetes, gout, amyloid, exophthalmic goiter, pregnancy and lipoid degeneration as examples of chronic nephrosis or "nephrodystrophy." We believe that it is necessary in each example of these conditions to know the extent of functional and associated chronic inflammatory lesion before reaching a conclusion as to whether the kidney is the seat of a nephrosis or of a chronic nephritis. Bell and Hartzell

regard the amyloid kidney as a special form of glomerulonephritis, but the number of cases in our experience in which there has been no severe depression of renal function, no elevation of blood pressure and no definite inflammatory changes in the kidney is such that we prefer to regard it as a type of chronic nephrosis. There is also much discussion as to whether or not the condition called acute parenchymatous or, more exactly, acute tubular nephritis, in which there is severe degeneration or even necrosis of epithelium associated with inflammatory edema of the interstitial tissues, should be regarded merely as a nephrosis. The severe functional depression of such lesions, both in experimental animals and in man, make it seem advisable to designate the condition acute tubular nephritis.

Aschoff so names it, but largely upon the basis of a more or less academic argument in favor of considering the epithelial lesions inflammatory. Grossly, such kidneys are like those of cloudy swelling except that they may be much larger and softer. Clinically, the term nephrosis includes a type of case which runs a prolonged course with marked edema, low blood pressure in the earlier stages sometimes subsequently elevated, urine of high specific gravity rich in albumin and casts (see Kaufmann and Mason). Anatomically, however, the kidneys as a rule show some degree of subacute or chronic glomerulonephritis often with marked epithelial degeneration.

Acute Nephritis.—All forms of acute nephritis show tubular degeneration or necrosis, but in variable degree. With the exception of acute tubular nephritis just discussed, some cases of acute interstitial nephritis, and so-called exudative nephritis to be discussed subsequently, all show some lesion of the glomerulus. Most of the cases of acute nephritis are properly qualified as acute glomerulonephritis. These are subdivided also as diffuse and focal. In the acute diffuse forms there may be, as indicated by Bell and Hartzell, degeneration of the glomerular tuft with hemorrhage, accumulation of leucocytes in the capillaries, or proliferation either of the capillary endothelium or the epithelium of the outer wall of Bowman's capsule. In order to present the matter in a systematic order, the whole group of lesions is outlined in the accompanying table and the discussion immediately directed toward the varieties of acute nephrosis.

First among the *causes* of acute nephritis are various infectious diseases, particularly those which show manifestations in the throat. Acute tonsillitis

CLASSIFICATION

NEPHROSIS

Acute

Chronic

NEPHRITIS

Acute diffuse glomerulonephritis

Degenerative

Exudative

Proliferative

Intracapillary

Extracapillary (subcapsular)

Acute focal glomerulonephritis

Healed focal glomerulonephritis

Acute tubular nephritis

Acute interstitial non-suppurative
nephritisAcute exudative non-suppurative
nephritis

Subacute diffuse glomerulonephritis

Chronic diffuse glomerulonephritis

NEPHROSCLEROSIS

Arterial

Arteriolar

of various kinds and scarlet fever are of great importance. To be grouped with these as causes are acute and subacute endocarditis and rheumatic fever. Although endocarditis appears to be a cause of acute diffuse nephritis it is, in its subacute form, the most important cause of acute focal glomerulonephritis. Diphtheria is said to rank lower than the diseases just mentioned, but on the basis of our experience its importance has been underestimated. Less frequent as causes, but of great significance, are surgical and other acute and chronic suppurations, puerperal sepsis, typhoid fever, dysentery, infectious enterocolitis of children, lobar pneumonia, typhus fever, purpura, malaria, etc. Nephritis is not rare in pregnancy perhaps because this state so reduces the resistance of the kidney that injurious agents, ordinarily harmless, produce damage. It may, however, be the effect of whatever agent produces the toxemias of pregnancy. Exposure to cold is thought by many to be of importance, but experimental investigation does not support this theory. The frequency of trench nephritis in the Great War and instances of nephritis in civil life, strongly suggest that cold predisposes to the disease. Prolonged physical exertion, as in long marches, may produce albuminuria but it has not been demonstrated that there is nephritis. Family disposition is suggested but not proven. It is possible that poor development and serious anomalies of the kidneys predispose.

Much *experimental work* has been done to elucidate the origin, course and effects of nephritis, admirably reviewed by MacNider. Attention has been directed toward certain poisons such as mercury, arsenic, lead, chromates, cantharidin, and uranyl nitrate. The first three of these are common poisons of man but the manifestations are usually those of nephrosis rather than nephritis. Except for the experiments of Bell with streptococci, Mallory and Parker with zinc and nickel, and MacNider with alcohol, it is doubtful that a nephritis in the strict sense of the word has been produced experimentally. Dietary and metabolic faults have been held responsible for chronic lesions, and Newburg describes lesions in rabbits resulting from high protein diets, but Miller shows that in rats, which are omnivorous, this regimen produces no renal lesions.

The gross morbid anatomy of acute nephritis is practically the same for all the forms described. In other words, it is impossible to distinguish these forms by naked eye examination. Occasional instances of acute nephritis occur in which the kidney grossly appears to be practically normal. Usually, however, the organ is enlarged, sometimes considerably, the consistence is reduced and the capsule is tense and strips with ease. The outer surface is smooth and may be pale gray, red or mottled in color. The organ cuts with reduced resistance and shows a soft, bulging, moist cut surface, which may or may not bleed freely, depending upon the accompanying hyperemia. The cortex is moderately or considerably thickened, the striations are obscured or broken, and the glomeruli instead of appearing as red points appear as grayish-white points, giving the cortex a sanded appearance. The pyramids may be slightly swollen but as a rule are practically normal. The peripelvic fat and pelvis are normal.

The microscopic appearance varies in accordance with the classification of acute nephritis given above. In all varieties of acute diffuse glomerulonephritis there are various retrogressive changes in the tubular epithelium, affecting particularly that of the proximal convoluted tubules. These include cloudy swelling, fatty degeneration, usually minor in degree, hydropic infiltration, hyaline droplet formation and necrosis. In some cases the desquamation of degenerated and necrotic epithelium is so great that the term desquamative nephritis is applied. Granular albuminous detritus is found in the tubules and also in the subcapsular space of the glomerulus. The casts found in the tubules are usually hyaline, which may show adherence of epithelium, of leucocytes, or of red blood corpuscles. In addition, finely and coarsely granular casts, epithelial, leucocytic, blood and fibrin casts may be observed. There may or may not be extensive hyperemia. Edema of the interstitial connective tissue is fairly common and occasionally there is slight infiltration of lymphoid and plasma cells. The lesions in the glomeruli, referred to as glomerulitis, distinguish the various microscopic forms of acute glomerulonephritis, the other lesions being essentially the same in all three forms. In degenerative glomerulitis, as described by Bell and Hartzell, there may be severe degeneration or necrosis of the cells of the glomerular loops, which permit of rupture of the capillaries and hemorrhage into the subcapsular spaces and thence into the tubules. Often the actual demonstration of degenerative lesions of the cells is difficult or impossible and is inferred by the presence of the hemorrhage. In exudative glomerulitis the capillaries show many polymorphonuclear leucocytes, and it is probable that they pass through the capillary walls and appear in the tubules and in the urine. Rarely the glomerular tufts may be converted into a small abscess. It seems probable that the accumulation of leucocytes is so great that circulation is impeded or completely stopped in the capillary loops, and it is stated that the leucocytes may remain in this situation after the process becomes chronic in character.

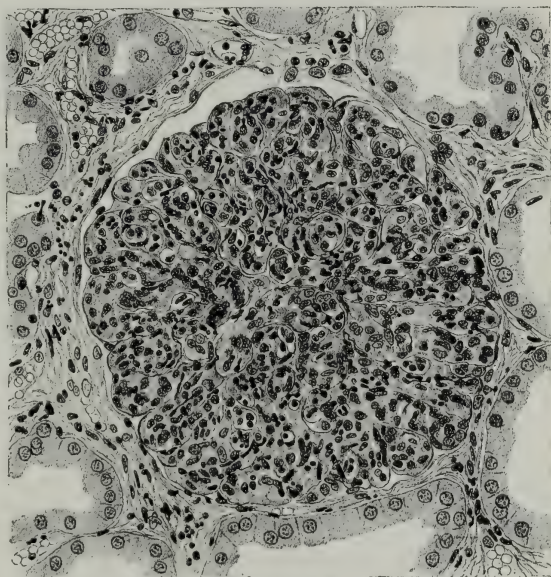


FIG. 322—Acute glomerulonephritis. The glomerular tuft is much enlarged by proliferation and swelling of its constituent cells. No blood is found in the capillary loops.

Proliferative glomerulitis is divided into two forms, the intracapillary form and the extracapillary or subcapsular form. In the intracapillary form the entire tuft is considerably enlarged and often occupies the entire capsular

space. The capillary loops are free of blood, due to swelling and proliferation of the capillary endothelium. Occasionally, a few polymorphonuclear leucocytes may be observed in the capillary loops and in the interstitial connective tissue. In the extracapillary or subcapsular form there is swelling and proliferation of the epithelium underlying the capsule of Bowman. The mass of cells may form a circular rim around the glomerulus or a crescentic mass. The tuft itself may be somewhat compressed by this proliferation. As a general rule, these forms of acute glomerular nephritis can be well distinguished from one another, but there are occasional cases in which confusion is likely and in which usually the final diagnosis is made upon the predominance of one change over the other.

Acute focal glomerulonephritis occurs presumably as the result of bacterial

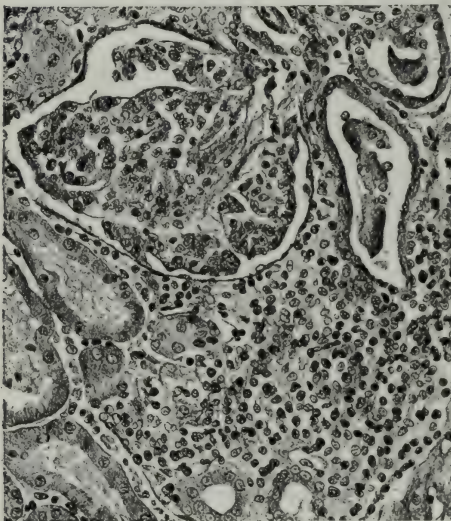


FIG. 323—Acute interstitial nephritis, showing extensive infiltration of mononuclear cells into the interstitial substance. The glomerular tuft shows acute glomerulitis.

emboli in the capillary loops, especially as the result of subacute bacterial endocarditis and possibly other infections. It is also suggested that it may be of toxic origin. The kidney usually shows no important lesion grossly but may be soft and swollen. The microscopic picture pointed out by Löhlein is well described by Baehr. The number of glomeruli involved is, in the majority of cases, much less than 40 per cent. and uncommonly may range between 50 and 75 per cent. The lesion may involve any part of the tuft and only occasionally the entire tuft. There is swelling of the epithelium with compression and obliteration of the capillaries, followed by necrosis of the swollen cells and

fusion to form a mass of finely granular material, sometimes containing a small amount of fibrin. In a few cases streptococcus anhemolyticus, the organism commonly found in subacute bacterial endocarditis, can be demonstrated in the capillaries. Blood may escape from the diseased glomeruli and appear in the urine. The granular mass is ultimately converted into fibrous tissue, the healed stage of the lesion. Most of the cases show various stages of the process. In the acute stages there is cloudy swelling of the tubules. In the later stages the tubules coming off from diseased glomeruli are atrophic, and about them may be some fibrosis and infiltration of lymphoid cells. The unaffected glomeruli appear to be normal.

It is usually considered that acute diffuse glomerulonephritis is due to the action of poisonous products of the infectious disease upon the cells, but many believe that since bacterial emboli may produce focal lesions directly, they may also produce diffuse lesions. The experiments of Pappenheimer, Hyman

and Zeman show that injected organisms appear to have a predilection for lodgment in the glomeruli, from which they rapidly disappear by phagocytosis. Nevertheless, an acute glomerulitis could be demonstrated after the disappearance of the organisms. On the other hand, glomerular lesions can be produced by soluble poisons, and the question as to which operates in human cases remains unsolved.

Acute tubular nephritis is an especially confusing form. Attention was called to it in discussing the nephroses. It shows in addition to severe de-

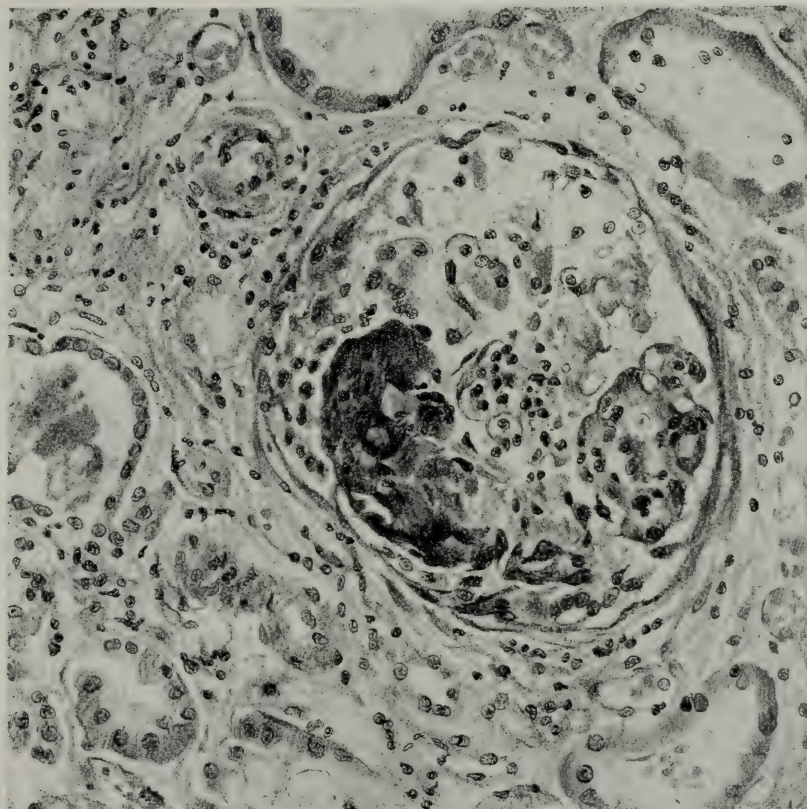


FIG. 324—Acute exudative nephritis, showing extensive fibrin formation in the subcapsular space, as well as swelling and proliferation of the capsular epithelium.

generation or necrosis of the tubular epithelium, an edema of the interstitial tissues of mildly inflammatory character. As a matter of practical fact, this name is given by many pathologists when there are also very slight infiltrative or proliferative lesions in the glomeruli. Both clinically and experimentally, acute tubular nephritis may produce severe clinical symptoms. Pathologically, it is often difficult to distinguish between this lesion and a simple nephrosis, and in such cases the final diagnosis is entirely a matter of personal opinion.

Acute interstitial non-suppurative nephritis, as described by Councilman, occurs as a complication of various acute infectious diseases. Grossly, the kidney in this disease almost constantly shows diffuse or focal redness in the

cortex. Microscopically, it is characterized by multiple foci, in the interstitial tissue near the blood vessels, of cells of the lymphoid series, such as lymphoid and plasma cells, which Councilman believes to be brought to the kidney from the lymphogenetic centers. These cells may be found in the tubules. Although occurring in other capillaries they are not seen in those of the glomerulus. Sometimes there are found large mononuclear cells with granular cytoplasm, referred to as myeloid cells. It is possible, as suggested by the experiments of Downey, that these are derived directly from the lymphoid cells. The tubules show various degrees of degeneration. The glomeruli, according to Löhlein, may show focal glomerulitis. It is often difficult to distinguish acute interstitial non-suppurative nephritis from early suppurative lesions.

Acute exudative non-suppurative nephritis is rare. It is characterized by the occurrence in glomerular tufts, subcapsular spaces, in tubular lumina and sometimes in the interstitial tissues of an infiltration of polymorphonuclear leucocytes in small numbers. There is a deposit of fibrin usually in very small amounts, but sometimes as fairly large clumps in the glomeruli or in the form of casts in the tubules. These lesions are focal in character and are believed by many to be the early stages of a suppurative lesion.

Subacute and Chronic Glomerulonephritis.—It was formerly customary to consider in the category of chronic nephritis, chronic parenchymatous nephritis, chronic interstitial nephritis, arteriosclerotic nephrosis and chronic passive hyperemia. Functional studies have shown that passive hyperemia is not of the order of lesion regarded as nephritis; cases which show serious functional and anatomical change are not merely passive hyperemia but have a superadded chronic nephritis. Pathogenetically and functionally, both forms of the arteriosclerotic kidney described in the section on circulatory disturbances of the kidney are excluded. What was formerly called chronic interstitial nephritis, meaning a small red granular kidney may be (a) arteriosclerotic nephrosis of arteriolar origin, a primarily contracted kidney, or (b) the end stage of a chronic glomerulonephritis, a secondarily contracted kidney. In the former there is no serious renal functional lesion and in the latter many of the signs and symptoms of chronic Bright's disease occur. Especially as the result of Löhlein's work, it is now known that the cases of so-called chronic parenchymatous nephritis, almost without exception, show chronic glomerular lesions, thus justifying the name chronic glomerulonephritis. Other forms of so-called chronic parenchymatous nephritis, in which there is admittedly no glomerular lesion but simply advanced tubular degeneration or necrosis with interstitial fibrosis, belong to the group of chronic nephroses.

According to the conceptions of Löhlein, nephritis or glomerulonephritis can be divided into three varieties or stages; namely, acute glomerulonephritis with a duration of days or weeks, subacute glomerulonephritis with a duration of one or several months, and chronic glomerulonephritis with a duration of a year or more. Many authorities have accepted this classification, but some prefer to regard the subacute form as an early stage of a chronic glomerulo-

nephritis. Most writers agree that the subacute and chronic forms are the outcome of an acute glomerulonephritis and are therefore of infectious origin. Others consider the possibility that a chronic glomerulonephritis may be of insidious onset and due perhaps to chronic toxic conditions such as gout, chronic infection, syphilis, lead poisoning, prolonged intestinal toxemias and all those conditions which may lead to fibrosis throughout the body. There is, however, reasonable doubt as to this point, and many regard the lesion of this order as belonging to the group of nephroses rather than glomerulonephritis. Ophüls states definitely that in so far as lead poisoning is concerned, the lesion in the kidney is an arteriosclerotic nephrosis.

In the *subacute stage* of glomerulonephritis, the kidney is still considerably enlarged. The consistency may be soft, as in acute nephritis, or there may be some firmness, depending in large part upon the overgrowth of connective tissue. The capsule usually strips with ease but may be slightly adherent. Kaufmann divides this stage into two forms, namely, the large white kidney in which the color is pallid throughout, and the large red or mottled kidney in which the color is a diffuse red, or the pallid kidney is mottled with areas of hyperemia or with small hemorrhages or both. It is doubtful that such a division is justified because microscopically the changes are fundamentally the same. The organ cuts with normal or very slightly increased resistance and shows a thick, bulging cortex, colored like the outer surface, with obscured striations and pale bloodless glomeruli. The pyramids may be somewhat swollen but usually only slightly so. The peripelvic fat and pelvic mucosa are normal. Microscopically, the tubular epithelium shows cloudy swelling and fatty degeneration, hydropic infiltration, hyaline droplet formation, necrosis and sometimes doubly refractile lipoid globules. The tubules may show all the varieties of lesion noted in discussing acute glomerulonephritis, and sometimes contain blood. The interstitial tissue may show edema, and infiltration of polymorphonuclear and eosinophilic cells. More important, however, is an early growth of connective tissue diffusely throughout the cortex which, in one of our cases, was massive. The blood vessels are essentially normal save for hyperemia. Hemorrhage may be observed in cases of mottled kidney. The glomeruli may resemble very closely those of acute glomerulonephritis. Following acute exudative glomerulonephritis there is likely to be some proliferation of connective tissue within the capillary loops, definitely enclosing the leucocytes. In the intracapillary forms the earliest change seen in the nature of chronicity is an increase in the amount of collagenous material between the endothelial cells, subsequently going on to definite fibrosis. The glomerular tuft may be distinctly lobulated and there may be adhesions between the tuft and the capsule of Bowman. In a general way, the subacute extracapillary glomerulonephritis is more severe clinically than the intracapillary variety. In the microscopic picture, the circles or crescents of proliferated subcapsular cells persist and show fusion, fibrosis and hyalinization. In this stage the fibrosis is more prominent in relation to the preëxisting connective tissue of the capsule of Bowman. Some of the glomeruli may show

more advanced fibrosis and hyalinization, and conversion into small balls of fibrous tissue with ultimate hyalinization.

In *chronic glomerulonephritis* the kidney is usually but not invariably reduced in size and weight. For descriptive purposes it is possible to divide this condition into two forms, the nongranular and the granular form of chronic glomerulonephritis. This does not mean that these are separate and distinct forms, or that the non-granular form may not change subsequently into a granular form. Nevertheless, the non-granular form may show considerable reduction in size of the kidney without granulation of the surface. As

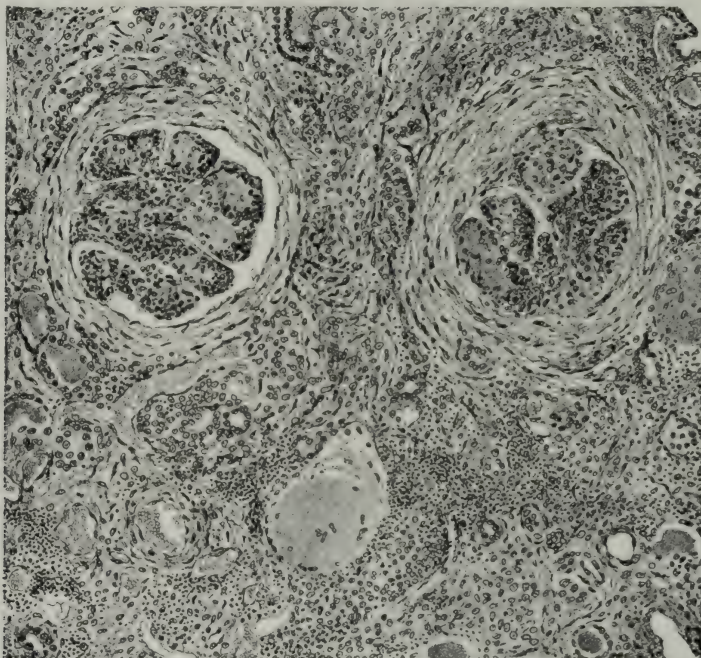


FIG. 325—Chronic glomerulonephritis, showing extensive fibrosis of interstitial tissue with associated infiltration of lymphoid cells. The glomerular capsules are markedly fibrosed. The tufts are the seat of extensive fibrosis and also focal fibroid areas, probably the scars of a focal glomerulitis.

a rule, in the non-granular form the reduction in size is slight or moderate. The organ is of increased firmness, the capsule strips with slight difficulty and discloses a generally smooth outer surface. The color may be pale gray or grayish-yellow, or may be spotted with areas of yellow several millimeters in diameter. In other cases the outer surface is red or mottled. The organ cuts with very slightly increased resistance and shows a slightly bulging or non-bulging, moist, slightly bleeding cut surface. The cortex is usually slightly reduced in thickness and shows color similar to that on the outer surface. The striations are blurred, broken and the tissue may be spotted or flecked with yellow. The glomeruli are generally pale and bloodless. The pyramids show no important change save for slight fibrosis near their tips. The peripelvic fat is often moderately increased in amount. The pelvic mucosa is normal. Microscop-

pically, it may be possible to observe a waviness of outline of the outer surface of the organ. The connective tissue shows a diffuse overgrowth, often with a slight infiltration of lymphoid and plasma cells. In other respects the microscopic appearance of these kidneys is closely similar to that to be described in the granular variety.

The granular form of chronic glomerulonephritis may show slight, moderate or marked reduction in the size of the kidney. In one of our cases, a man twenty-two years old, the kidneys weighed together sixty grams. The consistency and granulation of the kidney are in a general way in keeping with the reduction of size. The smaller kidneys are of leathery consistence. The capsule

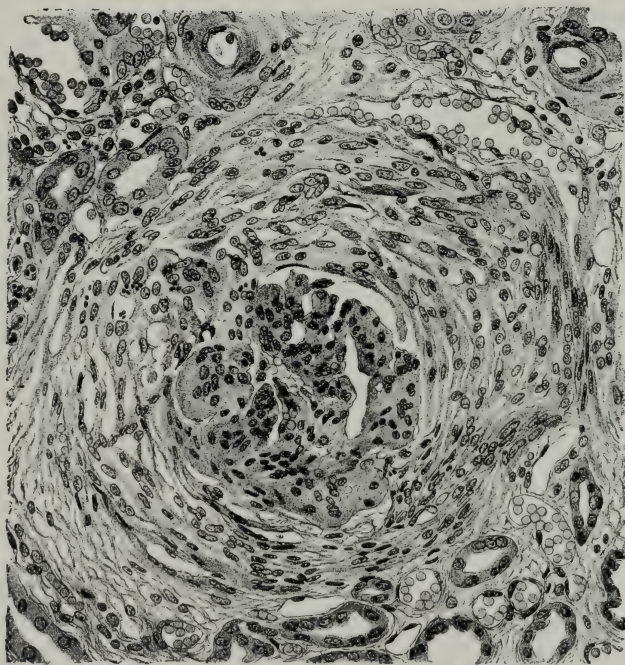


FIG. 326—Detail of subacute or subchronic capsular glomerulonephritis.

strips with difficulty, also depending upon the degree of fibrosis, and tears with it small pieces of kidney substance. The outer surface shows fairly uniformly sized projecting granules, although there is less uniformity than is observed in nephrosclerosis of arteriolar variety. The projections are composed of parenchyma and may be pale gray or yellow in color. In some instances, however, they are red. The retracted part is made up of connective tissue, usually of pale gray but sometimes of red color. In occasional instances the connective tissue network shows minute, glossy, yellow points made up of the fatty or lipoidal detritus of destroyed parenchyma. The organ cuts with increased resistance and in many cases retracts below the line of section. The cut section is firm and moist and of the same general color as the outer surface. The cortex is irregularly reduced in thickness, often shows lack of distinction from

the pyramids, and shows irregularity and blurring of the striations. The glomeruli are in large part pale and bloodless but some may be red. The markings of the pyramids are usually well preserved, but the entire substance of the pyramid is reduced in amount and the tips are almost always gray and fibrous. The peripelvic fat is usually considerably increased in amount. The pelvic mucosa is normal. Microscopically, the renal capsule shows considerable fibrous thickening. The interstitial connective tissue is diffusely overgrown, more especially in irregular focalized areas and in bands at right angles to the cortex. As a rule the glomeruli are not uniformly affected, presumably due to the recovery from acute disease on the part of a certain number of them. In the affected glomeruli there is usually fibrosis of the capsule and fibrosis of the glomerular tufts, more particularly near the center of the mass of loops. There may be fibrous adhesions between lobules of tuft and capsule. Sometimes small spaces are thus formed, which when lined by epithelium give a pseudo-acinar appearance. Depending upon the lesion in the acute stage, it may be possible to find a few leucocytes within the glomerular tufts or remnants of subcapsular epithelial proliferation, usually the seat of considerable fibrosis. Some glomeruli are converted into balls of fibrous tissue and others show partial or complete hyalinization. A number of glomeruli may show only thickening of the capsule with preservation of the circulation in the loops, others show general enlargement, and still others are essentially normal. The changes in the tubules vary greatly in degree and in situation. In the areas of fibrosis there is marked atrophy or complete disappearance of the tubules. In large part these represent the tubules leading off from glomeruli that are destroyed. In the places where fibrosis is slight, the tubules may show advanced cloudy swelling with thinning of the epithelial rim, fatty degeneration or necrosis. Not infrequently the tubules show considerable dilatation and even cyst formation, although to the naked eye examination cysts are not often visible. Reparative and regenerative processes can sometimes be observed. From older tubules new sprouts may project. Attempted regeneration of epithelium may result in the formation of multinucleated cells. It is only rarely that mitotic figures can be seen. Sometimes the scarred areas show small adenomata which probably represent an excessive epithelial regeneration. The blood vessels may be normal or may show severe lesions. The latter may be merely an intimal fibrosis, or there may be hyperplasia of elastica and fibrous tissue of the media with fatty degeneration in both media and intima. According to the studies of Ophüls, many of these vascular changes are due to an acute thrombovasculitis during the acute stage of the nephritis.

Functional Disturbances.—Although it is considered desirable to discuss at this time the disturbances of function in relation to nephritis, nevertheless, many functional alterations which appear in the non-suppurative forms of nephritis also are found to a greater or less degree in suppurative and in circulatory diseases of the kidney. The principal changes observed include alterations in the amount of urinary output, albuminuria, the presence of casts in the urine, hematuria, the retention or accumulation of nitrogenous waste,

the retention of salts and water, acid intoxication, uremia and increased blood pressure (see Oberling, Christian).

A decrease in the amount of urine excreted, oliguria, may result from reduced intake of water or increased output of water through other channels such as the skin and intestinal canal. It is common in passive hyperemia of the kidney due to disease of heart, lung or liver, or to obstruction of venous outflow. It occurs commonly in acute nephritis and in some of the acute nephroses. Although it is possible that under these circumstances it may be due to decreased permeability of cells of the capillaries in the glomerulus, yet there is little doubt that much of it is due to swelling of the parenchymatous parts of the kidney and accompanying reduction in circulation. The fact that stripping of the capsule of the kidney, the Edebohls operation, often relieves the oliguria lends strong support to this hypothesis. In chronic glomerulonephritis as well as in acute forms of glomerulonephritis, a reduction in the amount of urine may be accounted for by the suppression of circulation in a large number of glomeruli, due in the chronic cases to fibrosis and in the more acute cases to cellular infiltration and proliferation. The matter is bound up with the topic of salt retention and edema, to be discussed. In any of these cases the reduction of output may go on to a complete suppression of urine. Anuria may be due to obstruction of the ureter, bladder or urethra. In addition, there are nervous forms of anuria such as those due to operative procedures in the pelvis and other parts of the body. The surgical ligation of one ureter may produce suppression of urine from both kidneys, the so-called uretero-ureteral reflex. It is said that anuria may result from hysteria and perhaps from angioneurotic disturbances. Drugs, such as opium, reduce urinary output.

Increases in the amount of urine, polyuria, may be due to an increase of water intake or a reduced water output through skin and intestines. Polyuria occurs in diabetes insipidus, probably as the result of nervous influences, and in diabetes mellitus because of the presence of increased amounts of sugar in the blood and urine. It may be produced by drugs such as caffeine and by the injection of hypertonic salt solution. The removal of edema from the body tissues or from the body cavities may cause polyuria. It occurs in many of the forms of experimental renal disease. It is by no means common in acute nephritis but is sometimes observed in the very early and in the later stages. It occurs in chronic lesions, more particularly the arteriolar variety of nephrosclerosis, and in the later stages of chronic glomerulonephritis. The studies of Ghoreyeb show that kidneys the seat of these lesions allow perfusion fluid to pass through more rapidly than normal, which probably permits of an increased pressure within the capillary loops of the glomerulus. Assuming that fluid is resorbed in the tubules, their destruction in chronic nephritis may also account for the polyuria.

Albuminuria may rarely be due to large increases in the amount of ingested albumin, may be due to violent and prolonged exercise or exposure to cold. In animals, irritation of the bladder by foreign bodies and by inflammation

produces a "reflex" renal albuminuria (Evans, Wynne and Whipple). Of great importance is orthostatic albuminuria in which during the day, while the patient is standing or walking, albumin is present in the urine, and during the night or other periods of rest in the recumbent posture, there is no albumin. Only rarely are casts observed. Such patients may show a reduction in pulse pressure (Erlanger and Hooker, Gesell) but this does not explain the cause directly. According to Jehle, anterior curvature of the lower thoracic and lumbar spine is found in many such cases, and it is probable that by compression of the renal veins (Sonnen, Rieser) the circulation of the kidney is impaired. Passive hyperemia is a common cause of albuminuria. Richards points out that temporary local anemia produces albuminuria. All varieties of nephroses, nephritis and nephrosclerosis may be accompanied by albuminuria, although in the last named condition the amount is likely to be small. The

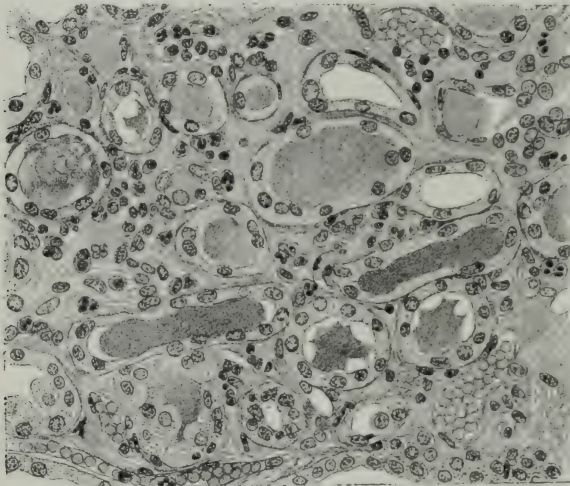


FIG. 327.—Casts in the renal tubules.

protein found in the urine is principally serum albumin, and it is highly probable that the albuminuria is due to increased permeability of the renal capillaries. In alimentary albuminuria the ingested protein may be identified in the urine by delicate immunological reactions. Inflammatory lesions and tumors of any part of the urinary tract may cause albuminuria.

The term cylindruria indicates the presence of renal casts in the urine.

These may be hyaline in character and upon the hyaline basis may be deposited fine or coarse granules of detritus, epithelial cells, leucocytes and erythrocytes. Casts may also be made up entirely of epithelial cells, leucocytes or erythrocytes, or mixtures of these, and occasionally are made up of fibrin. It is thought that casts may be composed of amyloid but the actual demonstration of this character is unusual. Nothing definite can be said as to the origin of the casts. It may be that they are formed by the extrusion of hyaline droplets from the tubular epithelium or the hyalinization of granular material which drops off from the diseased cells. It is also possible that casts may be formed from inspissation or precipitation of the dissolved proteins in the urine. If this were true, however, it would be expected that there would be a greater degree of uniformity between the number of casts and the degree of albuminuria than that which actually exists. The significance of albuminuria is variable, but when associated with cylindruria a definite lesion of the kidney is almost constant (Dublin).

Blood in the urine, hematuria, may be due to passive hyperemia, active hyperemia, inflammations, tumors, and traumatism in any part of the urinary canal. It occurs in acute glomerulonephritis, especially as the result of degenerative glomerulitis. In passive hyperemia it is probable that decrease in nutrition causes an increased permeability of the walls of the capillary loops.

In a variety of diseases of the kidney there may be a reduced capacity to excrete the end products of nitrogenous metabolism. This means a reduced output of these bodies in the urine and an accumulation of them in the blood. In order to make accurate determinations upon the urine it is necessary to collect a twenty-four hour specimen, but a determination of the amount in the blood gives essentially the same or more information. These examinations give a particularly good index of renal functional activity. In pronounced acute or chronic Bright's disease the total nonprotein nitrogen in the blood is usually increased. As a rule the urea nitrogen is increased more than the other fractions of the non-protein nitrogen. Myers and Killian believe that the reduction of permeability of the kidney for nitrogenous products affects first the uric acid, then the urea, and then the creatinin. This does not mean that in well established cases, however, there is necessarily a proportional increase of these bodies. Increases in nonprotein nitrogen are not necessarily an index of or an indication of the existence of an insufficient kidney, for as Mosenthal points out, "in the interpretation of an increased non-protein nitrogen of the blood in nephritis, four factors are to be considered: (1) retention of nitrogen by an insufficient kidney; (2) inspissation of the blood due to loss of water; (3) increase of protein catabolism; (4) the chemical combination in which non-protein nitrogen exists in the blood." Furthermore, such determinations give information of levels only at the moment of examination. Ambard and Weill, as well as McLean and Selling, have studied the rates of excretion of the non-protein nitrogen and have determined mathematical formulæ of the rate of excretion, which is a somewhat more accurate method of expressing the ability or inability of the kidney to excrete urea and chloride than is the determination of these products in the blood alone. In certain stages, presumably early, of human nephritis, and in the earlier stages of experimental nephritis, notably that produced by uranium, a condition of excessive secretion of nitrogenous metabolites, or superpermeability, may appear. Under these circumstances the total non-protein nitrogen of the blood may be reduced. Of the metabolites mentioned above, none can be said definitely to be the cause of the symptoms of Bright's disease. In summary, it may be said that accumulation of nitrogenous metabolites in the blood is a common condition in Bright's disease, and that this accumulation is shared by the various metabolites in somewhat different degree; that whereas in certain cases those metabolites which are excreted with difficulty show earlier accumulation and those secreted with ease show lesser accumulation, yet the well marked cases show considerably greater accumulations of urea than of any other part of the non-protein nitrogenous material (Hewlett, Karsner).

A ready means of determining the functional capacity of the kidney is to

test its ability to excrete certain ingested or injected substances, such as the dyes phenolsulphonaphthalein and indigocarmine and other substances such as salt and lactose. In a general way the inability of the diseased kidney to excrete dyes more or less closely parallels its inability to excrete nitrogenous metabolites. Of similar importance is the ability of the kidney to excrete amylase (Fitz).

The reduced ability of the kidney to excrete salt is more or less intimately bound up with the subject of water retention and edema. This refers principally to sodium chloride. Nevertheless, as shown by Denis, phosphates and sulphates may be retained in nephritis. Magnesium, potassium and calcium are not retained. Certainly, if water be retained, a certain amount of salt must be retained in order to preserve isotonicity, and conversely, if salt be retained, water should also be retained in order to preserve isotonicity. This rule, however, is not invariably followed in kidney disease. After a certain level of water retention has been reached, edema appears, and is observed first in the loose tissue such as the lower eyelids, then more generally over the body surface and also in the body cavities. The edema of acute or chronic glomerulonephritis is more widespread and less dependent upon gravity than is that of chronic heart disease. In certain cases the degree of water retention in the body can be shown to be generally proportional to the amount of salt administered. Thus, the retention of water in these cases must be secondary to the salt retention. Occasional cases of salt retention occur in which no edema is observed. It seems unlikely that water retention is ever primary. In some cases of water retention the amount of water in the blood produces a hydremia which the kidney seems unable to relieve. Similarly, salt may accumulate in the blood in larger amounts than normal. Thus, the failure of the kidney to secrete salt and water is not due to diminished amounts brought to it by the blood (see Loeb). The experimental introduction of large quantities of water may produce a hydremia, more marked than is ordinarily seen in Bright's disease with edema, without producing edema in the animal. Whereas the studies of Epstein and of Claussen indicate that the osmotic pressure of the plasma proteins is decreased, therefore favoring a movement of water toward the tissues, studies of electrolyte concentration have been contradictory (Marrack). There is little evidence to support the hypothesis that vascular permeability is increased except the fact that vascular poisons seem to favor development of edema. It is not probable that acid intoxication is of importance in the production of edema of Bright's disease (McLean), because such acid intoxication is not demonstrable as a rule until late in the course of the disease.

Acid intoxication may appear in the course of nephritis. While in the earlier stages of nephritis acid intoxication is unusual and nitrogen accumulation in some form or other fairly common, when uremia appears acid intoxication is in variable degree almost constant. Occasional cases occur in which accumulation of nitrogen cannot be demonstrated. It is therefore apparent that there is no parallelism between the degree of acid intoxication and non-

protein nitrogen accumulation in any stage of nephritis except in uremia (Peabody), and even in that condition wide variations may be found. It is uncommon for the acidosis of Bright's disease to show an associated ketosis.

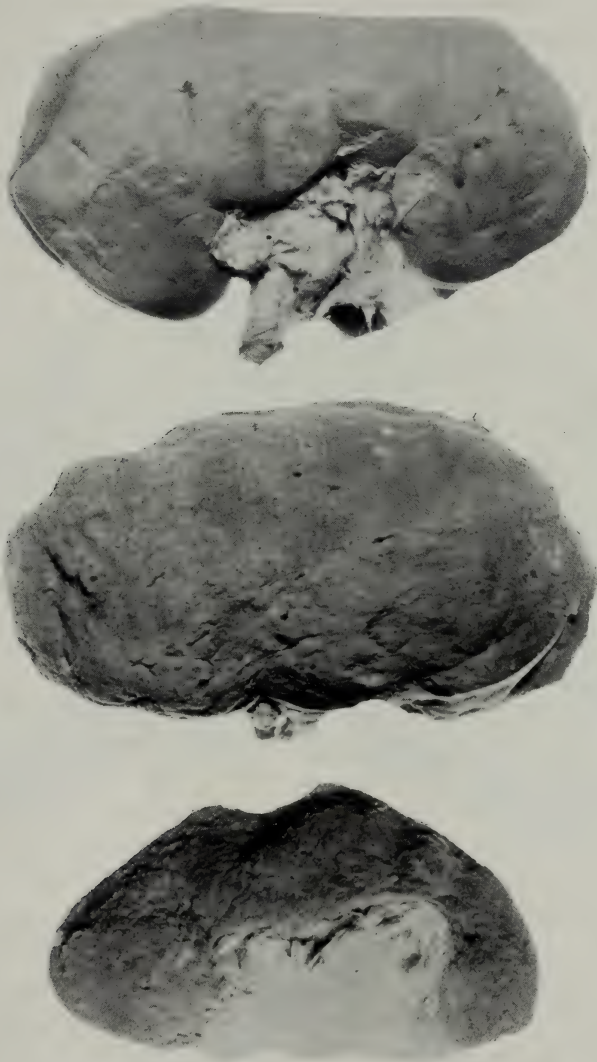


FIG. 328—Varieties of glomerulonephritis. Above is a much swollen soft pale kidney of acute glomerulonephritis. Next is a kidney somewhat reduced in size with a few fibrotic areas and a mottled outer surface, the kidney of subacute glomerulonephritis. Below is the terminal stage of glomerulonephritis, small and with irregular retractions, often to be differentiated from the arteriolar arteriosclerotic kidney only by microscopic examination (uniform reduction).

Fischer and also MacNider take the view that acid intoxication or decreased reserve alkali may in itself produce Bright's disease. The experiments of Karsner, Reimann and Brooks would indicate, however, that the demonstrable acid intoxication in nephritis is secondary rather than primary.

The term uremia cannot be exactly defined, but is usually understood to refer to a symptom complex occurring in the course of renal disease and including disturbances of the nervous system such as headache, coma, convulsions, disturbances of the alimentary tract, particularly diarrhea, disturbances of circulation, particularly high blood pressure, and respiratory disturbances, especially increased ventilation. The alimentary disturbances are often due to an acute enterocolitis in the ileocecal region, caused possibly by excretion of irritant substances through this part of the gut. The increased respiration or increased ventilation of the lung is probably due to acidosis. It is supposed that uremia taken as a whole represents some sort of intoxication, either the result of accumulation in the body of substances that should normally be excreted by the kidney, or the result of the formation of toxic



FIG. 329—Multiple retention cysts in arteriolar arteriosclerotic nephrosis.

substances in the body. As pointed out above, the accumulation of non-protein nitrogenous material is extremely common in Bright's disease and it occurs in practically all cases of uremia. Nevertheless, occasional cases of uremia are observed in which the non-protein nitrogen is not materially above the normal. The older conception that uremia is due to urea was for many years abandoned, but the experiments of Hewlett and his collaborators showed that if an amount of urea be ingested, sufficient to raise the level in the blood above 160 mgm. per 100 c.c., headache and other nervous symptoms ensue. Experiments of Leiter strongly support the idea that accumulation of urea is of great significance. By intravenous injection of urea into dogs he was able to produce symptoms very closely resembling those of the convulsive type of uremia in man. There still remains the question as to whether or not a poisonous product may occur. Foster has found in experimental animals that in cases with convulsions but without marked increase in the total non-

protein nitrogen in the blood, there is present a poisonous body called urinod, which is capable of producing these symptoms. As yet, however, this has not received extensive confirmation or wide acceptance. Golla, in an exhaustive examination of the subject, suggests that trimethylamine causes the trouble, but gives no final proof. These topics are admirably discussed by Hewlett, by Wells and by Austin.

High blood pressure, hypertension, may occur in moderate degree in acute nephritis and is fairly common in the later stages of chronic glomerulonephritis, with resultant cardiac hypertrophy. It is also associated with arteriolar nephrosclerosis, in which it is due to the widespread arteriolar disease rather than that in the kidney. In glomerulonephritis it has been supposed that the high blood pressure is due to lesions of the glomeruli. The complete occlusion of renal circulation does not produce any prolonged elevation of blood pressure, and it is unreasonable to assume that occlusion of that in the glomeruli may do so directly. Anderson has shown that removal of 70 per cent. of the kidney tissue of rabbits "does not produce hypertension even when prolonged renal insufficiency results." Indirectly it is possible that the lesions of the glomeruli, perhaps also of other parts of the kidney, are responsible for accumulation within the body, or production within the body, of substances that can produce elevation of blood pressure. There is no definite proof that increases in adrenalin output can produce continued elevation of blood pressure (Mosenthal). It is equally true that increases in protein intake do not produce elevation of blood pressure (Strouse and Kelman) nor does the retention of salt play any important part (O'Hare and Walker). Pearce was unable to demonstrate that any internal secretion of the kidney, even though it exist, could produce this change. Although several authors, notably Shaw, have found that extracts of kidney tissue may produce a temporary elevation of blood pressure, the experiments of Pearce would indicate that tissue extracts and the urine of the dog produce depression of blood pressure. Urea, uric acid and creatinin do not produce permanent elevation of blood pressure but there remains that fraction of non-protein nitrogen referred to as residual or undetermined nitrogen in which are included various amino-acids. Croftan reports that the alloxuric bases, xanthin and hypoxanthin, are capable of producing a rise in arterial pressure. Major has found that in certain cases of hypertension the excretion of one of these amino-acids is reduced, and experimentally that the injection of properly estimated doses of salts of methylguanidin and of guanidin produce prolonged elevation of blood pressure. He states that, "it seems quite possible that kidneys badly damaged by chronic nephritis or only slightly damaged by arteriosclerosis or by a small vessel sclerosis might be unable to excrete properly these substances," but as yet the results have not been widely confirmed.

Disturbances of the nervous system including functional changes such as headache, neuralgia, coma, convulsions, diplopia, amaurosis, etc., are not in most instances associated with definite pathological lesions but are thought to be due to local edema, and vague action of supposed poisonous substances.

Paralysis may be severe but transient, and is explained on the same basis. The hypertensive cases may show severe and fatal hemiplegias due to cerebral hemorrhage. In reference to the organs of special sense there is little that is definite. Ringing in the ears may be due to anemia and to hypertension. Transitory deafness can be grouped with the unexplained lesions mentioned above. The so-called albuminuric retinitis has a fairly definite morphology and may produce partial or complete blindness. There are white or yellow spots around a somewhat swollen nerve head and around a hyperemic macula, edema of the retina, sometimes an inflammatory exudate upon the retinal surface, narrowed and beaded sclerotic arteries, distended veins and multiple hemorrhages. It is most frequently associated with the small, red, granular kidney with hypertension, the arteriolar nephrosclerosis. It occurs less commonly in chronic glomerulonephritis, in acute glomerulonephritis and the nephritis of pregnancy. It is supposed to be due to degenerative lesions of the retina resulting either from direct toxic influence or vascular lesions, but Volhard's view, supported by Schieck, is to the effect that there is a primary vasoconstriction with local retinal ischemia, followed by endothelial proliferation in the arteries and permanence of the retinal ischemia with associated circulatory, inflammatory and hemorrhagic changes.

A study of the data presented above will show that Bright's disease affects many parts and mechanisms of the body, and that it is to be regarded as a general disease. As a striking manifestation of this proposition is the occurrence of anemia in Bright's disease, more especially in chronic glomerulonephritis. A high percentage of such cases show moderate reduction of number of erythrocytes with generally proportional reduction of hemoglobin. Extreme reductions sometimes occur. The leucocytes are usually normal in number or only slightly increased, although in uremia there may be a distinct leucocytosis. There is often a fairly close parallelism between accumulation of non-protein nitrogen and anemia. The studies of Brown and Roth on cases of chronic glomerulonephritis, in which hemorrhage, sometimes a cause of anemia in acute nephritis, was excluded, indicate that neither hemolysis due to retained products of metabolism or to toxic agents, dietary deficiency, nor loss of protein in the urine is the cause. They ascribe the anemia to decreased functional activity of the bone marrow as a part of the general and widespread damage in the disease, as a sort of parallel to the injury to heart, vascular system and retina.

Suppurative Inflammation.—Bacteria may gain access to the kidney through the blood stream, by ascending infection from bladder, ureter, renal pelvis or kidney itself, and by direct trauma to the kidney.

Hematogenous or metastatic suppurative nephritis occurs as the result of acute endocarditis and of septicemia and pyemia, incident to infections in various parts of the body. The bacteria, usually either streptococci or staphylococci, lodge in the capillary loops of the glomeruli, or less commonly in the capillaries between the tubules, and produce multiple small abscesses. Grossly, such a kidney is usually swollen, hyperemic and soft. The capsule strips

easily but may tear with it the outer wall of superficial abscesses. The outer surface shows numerous small abscesses, one to several millimeters in diameter, scattered diffusely over the surface or sometimes arranged in small groups. The abscess itself is white or pale yellow and soft, and from it can be expressed pus. There is usually a surrounding area of marked hyperemia. The organ cuts with normal resistance and shows a slightly bulging, soft, swollen, hyperemic, bleeding cut surface. Usually the abscesses are found principally in the somewhat thickened bulging cortex, but occasionally they are found also in the medulla and in rare instances they are confined to the pyramids. Microscopically, it is not uncommon to find a clump of bacteria in the center of the abscess, and if the condition be sufficiently early the organisms may be found in the glomerular loops or sometimes in the intertubular capillaries. Around the bacteria there is an area of necrosis, surrounded immediately by a rich



FIG. 330—Multiple embolic abscesses in a kidney which also exhibits fetal lobulations

infiltration of polymorphonuclear leucocytes, grading off into an area of intense active hyperemia. The tubules are usually the seat of advanced cloudy swelling, sometimes with fatty degeneration and with necrosis. Hemorrhage into the interstitial tissues, as well as into the tubular lumina, is not uncommon. The glomeruli not affected by the bacteria may be the seat merely of a hyperemia or may show any of the forms of acute glomerulitis. Two other sub-varieties of hematogenous suppurative nephritis include that form where, instead of bacteria lodging in capillaries, there are thrombi infected with bacteria lodging in arteries, followed by the production of infarcts which subsequently become suppurative. The same condition may follow a suppurative endarteritis from invasion of vessels by abscesses. Also of importance but not very common is that form in which, whether abscesses form in the glomeruli or not, the destruction of the glomeruli may permit the bacteria to gain access to the urinary stream, subsequently to lodge in the collecting tubules in the pyramids. In this form, without definite lesion in the renal pelvis, there are found streaks of suppuration radially disposed in the cut section of the pyra-

mids. These streaks show a central collection of pus, and necrotic material surrounded by reactionary hyperemia. This form is often referred to as the excretion form of hematogenous suppurative nephritis.

In contrast to the hematogenous or metastatic variety of nephritis there is the so-called ascending or urinogenous form of suppurative nephritis, sometimes referred to as the surgical kidney. Grossly, the kidney shows all the signs of advanced cloudy swelling and may be markedly enlarged. In cross section the renal pelvis is the seat of suppurative inflammation, with or without distention of the cavity. Radiating from the tips into the substance of the pyramids, there are streaks of pus with a surrounding area of hyperemia. Sometimes these extend outward into the cortex and may even pass through the cortex to produce perinephric abscesses. Microscopically, the changes are found principally in the pyramids. The central area of necrosis is surrounded by infiltration of polymorphonuclear leucocytes and mononuclear cells and then by an area of hyperemia. The tubules may contain masses of leucocytes

sometimes sufficiently solidified to form casts, and in some instances bacteria can be identified in the tubular lumina and in the lining cells. Most such cases have their origin in a suppurative cystitis which ascends through the ureter, involves the renal pelvis and then the kidney. The organism particularly associated with this condition is the colon bacillus but others are occasionally found. Various hypotheses have been advanced as to the origin of such infection. It has been thought by

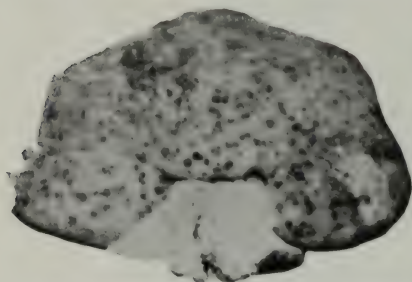


FIG. 331—Child's kidney, the seat of pyemic abscesses and petechiæ (staphylococcus pyogenes aureus).

some that the organisms in the bladder gain access to the blood stream and are then subsequently deposited, perhaps by a process of tissue selectivity, in the renal pelvis. Much better supported is the assumption that the organisms gain access to the pericystic lymphatics and, following the natural route of drainage, the infection extends through the lymphatics of the ureter to those of the pelvis with inflammation in the lymphatics, which extends to the ureter and pelvis. This view is supported by the extensive investigations of Sweet, of Eisendrath and Schultz, of Sugimura and their collaborators. As against this is the fact that human cases are discovered in which the inflammation is confined to the lining of the ureter and pelvis, and does not involve particularly the surrounding lymphatics. The fact that reverse peristalsis does not occur in the ureter has made it seem likely that infection cannot ascend through the lumen of the ureters from the bladder upward. The studies of Graves and Davidoff, and Eisendrath, Katz and Glasser, make it clear that when the neck of the bladder is obstructed, as is likely to occur in acute inflammations of the bladder and under other circumstances such as enlarged prostate and calculus of the bladder, positive pressure upon the wall of the bladder will result in backflow of urine into the ureters.

It is probable that this is one method for the ascent of infectious agents. By paralysis of the ureters and section of the ureterovesical valves, Barber and Draper produced ascending infection through the ureteral lumen.

In hematogenous suppurative nephritis, patients usually die because of the nature of the causative disease, but in ascending suppurative nephritis occasional recoveries occur. Under these circumstances scars may be found in the kidney resulting from the healing of the abscesses. If visible grossly, there may be a central portion of yellow color due to the fatty and lipoidal detritus of destroyed kidney substance.

Perinephric Inflammations.—The most important inflammations in this region are abscesses, referred to usually as perinephric abscess, or tautologically as perinephritic abscess. Probably the most frequent cause is extension from abscesses in the renal cortex, which infiltrate between kidney and capsule, invade the capsule and then extend to the paranephric tissues, especially the fat. Of Hunt's 106 cases, nineteen were secondary to renal infection, twenty-eight to calculi, tuberculosis, tumor or traumatic injury of the kidney, and fifty-nine showed no primary lesion in the kidney. Abscesses of extrarenal origin are usually paranephric but may extend into the capsule and kidney. These lesions may be secondary to suppurations of vertebræ, intestines, internal genitalia, pleura and other neighboring organs, or to pyemia.

Fibrosis of capsule and paranephric tissues may occur as the result of acute inflammations in that region, or probably also as secondary to renal suppuration. Contraction may compress the kidney and depress its function. O'Connor regards it as a chronic inflammation, chronic cicatrizing perinephritis, but it may be merely a scarring of the acute lesion, or perirenal sclerosis.

Tuberculosis.—Infections of the kidney by tubercle bacilli may follow the same routes as those indicated for pyogenic organisms. Tuberculosis of the kidney in massive form may be rarely the result of direct extension of tuberculosis of neighboring structures, particularly of the spinal column. The hematogenous variety of renal tuberculosis is miliary and is common as a part of generalized miliary tuberculosis. The miliary tubercles, sometimes minute but sometimes attaining a diameter of 2 mm. or more, as a rule are distributed in the cortex and are visible both upon the outer surface and in cut section. Tubercle bacilli may pass through the capillary loops of the glomerulus and lodge in the collecting tubules to produce an excretory form of tuberculosis of the kidney. In these cases the tubercles appear as elongated streaks, which when they have attained a certain size may show daughter tubercles in the neighborhood. It is sometimes possible microscopically to find shadows of original tubules in the center of such tuberculous masses, and in the lumina of these tubules collections of tubercle bacilli. This form is of especial importance since it may lead to tuberculous infection of the renal pelvis and lower genito-urinary tract. If such a tuberculosis of the renal pelvis cause occlusion of the orifice of the ureter, there may be damming back of urine and of caseous material in the pelvis with subsequent distention and an extension of the infection into the kidney itself, producing a form of tubercu-

losis resembling very closely the ascending variety. Nevertheless, extensive involvement may occur without obstruction, and in some of these cases there may be a polyuria which is believed to be due to the destruction of the concentrating activity of the tubules of the medulla. Ascending tuberculous infection of the kidney may originate in the seminal vesicle or the epididymis and then spread to the prostate, bladder, ureter, and renal pelvis. As a rule, it produces obstruction in the ureter with distention of the renal pelvis. The tuberculous process then extends through the pyramids in radiating lines into the cortex. In massive involvement, the neighborhood of the greater tuberculous areas shows daughter tubercles. More particularly when there is

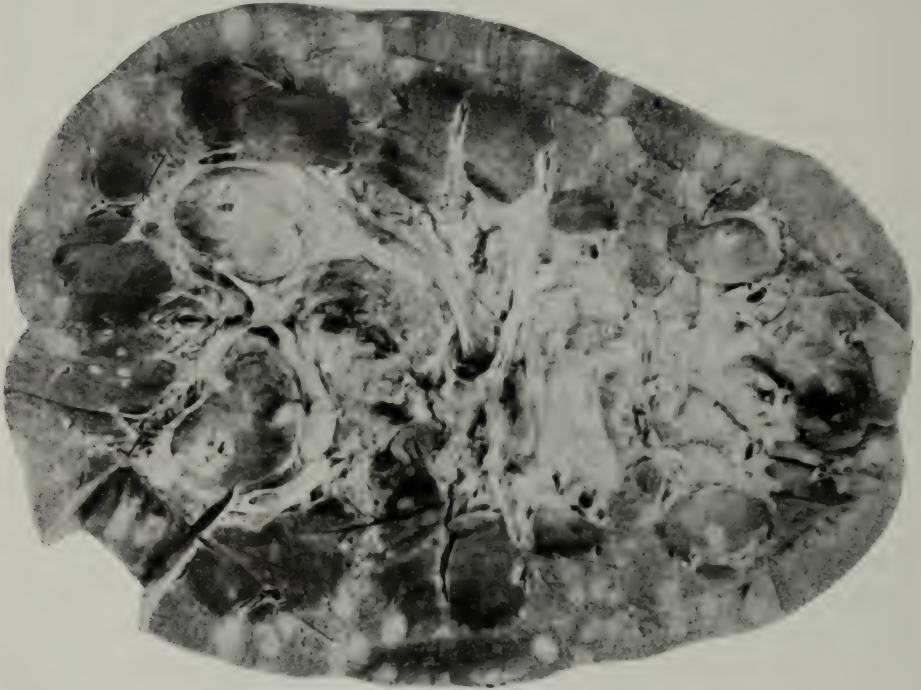


FIG. 332—Cut surface of kidney with numerous hematogenous tubercles.

obstruction of urinary outflow, the kidney may be converted into a large caseous mass. Thus, the pyramids are partially or completely destroyed by the tuberculosis and only a thin rim of the cortex may remain. Before obstruction is complete, there may be excavation of the mass so that the kidney is made up of a connective tissue shell with a small part of parenchymatous substance, and the pelvis is connected with numerous large tuberculous cavities. The presence of neighboring daughter tubercles is helpful in the diagnosis. This form of the disease, sometimes called renal phthisis, is almost invariably chronic in nature and associated with a good deal of fibrosis. Hematogenous or miliary tuberculosis is usually acute in character as is true also of the excretion form, but as a rule the ascending variety of renal tuberculosis is subacute or chronic. Rarely, vascular involvement by tubercles

may lead to infarction of the kidney with subsequent spread of the tuberculous infection, leading to a tuberculous infarct. Neighboring daughter tubercles assure the diagnosis. An excellent review of the subject of renal tuberculosis has been made by Quinby.

Syphilis.—Gummata of the kidney occur, but are rare, both in acquired and congenital syphilis. In congenital syphilis, defective development and degenerations and inflammations in the kidney, may occur, but a large majority of syphilitic fetuses show no lesions of the kidneys. Falci has demonstrated in congenital syphilis such changes as slight diffuse fibrosis, foci of mononuclear cells apparently mesoblastic remnants, underdevelopment of tubules and of Malpighian bodies with areas of hyalinization of glomerular loops, outspoken focal glomerulonephritis and small collections of cells suggesting multiple miliary gummata. Warthin finds numerous spironemata in both congenital and acquired syphilis and believes that in the septicemic stage spironemata are excreted into the urine. Syphilis may lead to interstitial edema and focal accumulations of mononuclear cells in both congenital and acquired forms. Focal infarct-like scars are ascribed by some to both forms of syphilis. Florid syphilis may be complicated by acute nephrosis or even glomerulonephritis (Karvonen; Stengel and Austin) but this is not a specific lesion and may be caused in some cases by the therapy.

Actinomycosis of the urinary tract is rare (Cecil and Hill).

Regeneration.—Evidences of epithelial regeneration in the kidney are not uncommon. More particularly in diffuse diseases of the kidney, according to Tilp, multinucleated cells, new epithelium identified by hyperchromatic nuclei and poorly stained cytoplasm, and occasional mitotic figures are observed. Similar changes have been described by MacNider near infarcts. Tubular arrangement of newly formed epithelium may occur around focal lesions but is rare in diffuse lesions. Epithelial growth has been observed in tissue culture by Fleischer and Loeb; with tubule formation by Carrell and Burrows and by Drew. Increasing age of the individual decreases the power of regeneration. New formation of Malpighian bodies does not occur, although extensive destruction of glomeruli in chronic disease may be accompanied by an apparent enlargement of remaining glomeruli.

Tumors.—The most common benign tumor of the kidney is the fibroma, which occurs as a single nodule or several nodules in the pyramids, typical in structure and usually only two or three millimeters in diameter. Lipoma may also occur in the same position but is said to be somewhat more frequent in the cortex. Adenoma of the kidney may occur apparently as the result of regeneration following chronic fibrotic diseases of the organ. In such instances they appear as minute, pale yellow, well defined, slightly bulging areas and are found in small scarred spaces of the kidney. Histologically, they are often poorly defined and show many small acini, sometimes with slight papillary ingrowth. The cells are small and cuboidal in shape. The adenomas believed to be of embryonal derivation are usually single and in the cortex but may be multiple. They are usually several millimeters in size, well defined and of pale

or bright yellow color. Histologically, three forms are recognized by Dunn. The tumor mass may show a definite capsule both grossly and histologically. In one form the cells are believed to represent displaced remnants of adrenal cortical substance, and show parallel rows of large vesiculated cells resembling in cell form and in arrangement adrenal cortex. Another form shows simple acini lined with small cuboidal cells or, what is more frequent, papillary in-growth in the acini. The third form is the papilliferous cyst, lined by cuboidal cells; numerous papillary outgrowths spring from the walls to fill the entire cavity. Practically all of these tumors are benign, but occasionally metastasis may arise without there being any definite indication of malignancy in the original tumor.

The so-called *hypernephroma* represents the most common tumor of the adult human kidney. According to the hypothesis of Grawitz this originates from misplaced fragments of adrenal cortex, which may remain quiescent as in the adenoma spoken of above, or may become malignant to produce the hypernephroma. Stoerck, Frazer and others take exception to this view, and after careful examination of a large number of tumors express the opinion that practically all such tumors are derived from adenomata which in turn take origin from renal epithelium. The fact that such tumors are sometimes observed as primary growths in the lower genital tract and also in the lower part of the liver, makes it seem probable that many of them are truly of the nature ascribed to them by Grawitz. Such tumors usually originate in the

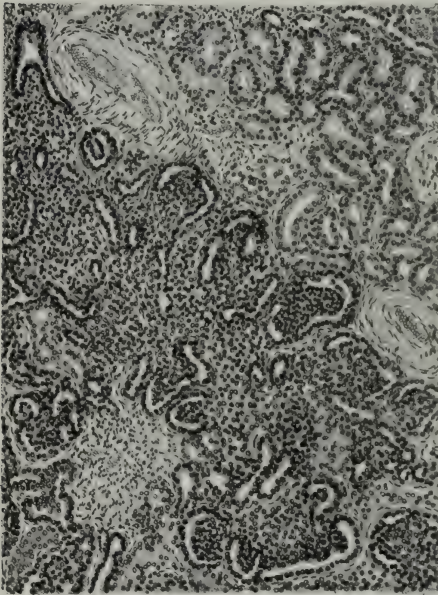


FIG. 333—Adenoma of the kidney.

upper pole of the kidney, progressing from that situation to involve a large part of the organ, sometimes destroying it completely. The tumor is usually partially encapsulated and in its growth displaces as well as invades tissue. It is a soft, smooth or nodular mass of yellow or mottled yellow, gray and red color. The cut section is soft, bulging, of yellow or mottled yellow and red color, bleeds freely and often shows numerous areas of hemorrhage and necrosis. Microscopically, the tumor is usually rich in large cuboidal cells and poor in connective tissue, and somewhat denser bands separate the mass into small lobules. Covering the connective tissue framework and extending into the spaces in papillary form, sometimes with multiple division of the papillary network, are large cuboidal cells with richly vesicular cytoplasm containing fat and glycogen. The cells are often in parallel rows growing out from the framework. The nuclei are small and stain well. Mitotic figures are not com-

mon. As pointed out in the chapter on tumors, it is doubtful that adrenalin has been demonstrated in these tumors. Although this histological description may be regarded as fairly typical, Stoerek maintains that all types of cell between the large vesicular cell and the small cuboidal cell of the renal adenoma can be found in numbers of specimens. Without further investigation of the subject, it can only be said that in our opinion the hypernephroma in a large number of cases represents a growth from misplaced adrenal tissue, but that confusing forms of carcinoma are not uncommon. Metastasis is almost invariably by the blood stream and appears primarily in the lung. A more widespread distribution may occur, including bones, liver, skin and other tissues. Indeed cases are sometimes diagnosed by the examination of subcutaneous nodules. As the tumor grows into the kidney it is likely to invade

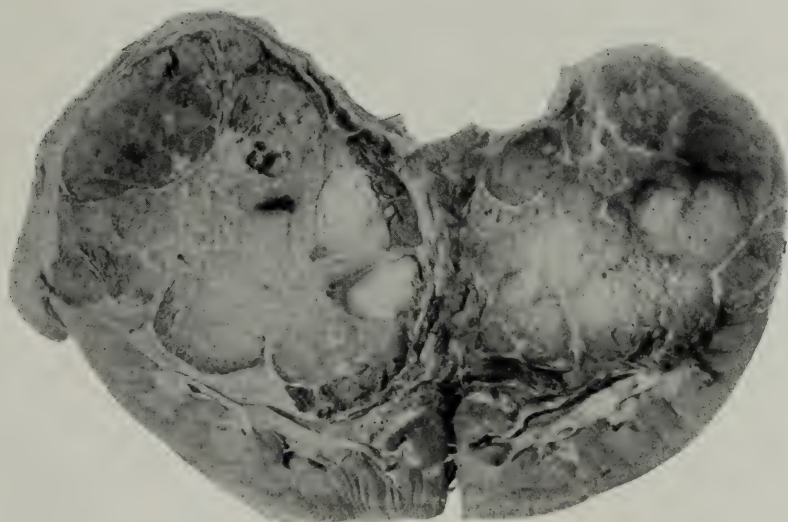


FIG. 334.—A kidney split open to show extensive hypernephroma of upper pole.

the veins and produce extensive tumor thrombosis (Goodpasture and Jacobson). Partial obstruction may be accompanied by distal distention of the veins. Involvement of the renal pelvis may produce hematuria, either mild or severe, and is said to occur at some time in a large percentage of cases.

Carcinoma occurs either as a carcinoma simplex or as an adenocarcinoma originating presumably from adenoma. In some cases, however, the tumor appears to originate in the lining of retention cysts. These must not be confused with carcinomata originating in the renal pelvis. Primary sarcoma in the form of spindle cell sarcoma or lymphosarcoma is distinctly unusual.

The congenital mixed tumor, or as it is sometimes called, the embryonal adenosarcoma, occurs principally in early life. It is usually unilateral, involves almost the entire kidney substance and may attain very large size. Grossly, it constitutes a firm, fairly well encapsulated, lobulated mass. The cut section usually shows a variegated appearance in which pale and dark red areas, sometimes intermingled with areas of necrosis, are scattered irregularly.

Microscopically, there are found masses of connective tissue, sometimes typically fibromatous and sometimes typically sarcomatous. Frequently, there are numerous small acinus-like collections of cells resembling those of renal epithelium. Whether these cells originate from the upgrowth of primary ureter or from nephrogenic tissue cannot be positively stated. Intermingled with connective tissue, or constituting fairly definite areas in themselves, there may be found cartilage, bone and the embryonal type of striated muscle. Other types of tissue are less frequent. Such tumors may grow to very large size without metastasis, but their histological character usually places them with the malignant tumors.

The secondary tumors, both carcinoma and sarcoma, are usually carried to the kidney by the blood stream, with the production of numerous metastases.

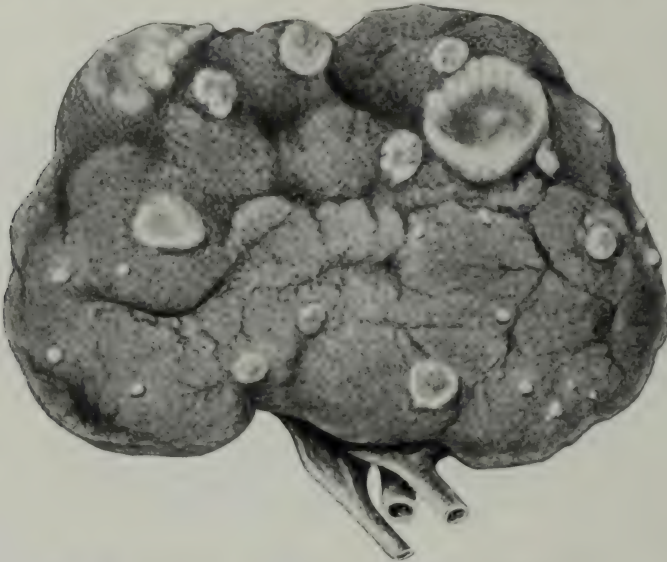


FIG. 335.—A kidney, the seat of multiple metastatic carcinoma.

The lymphatoma of lymphatic leucemia must be carefully differentiated from masses of lymphosarcoma in the kidney.

Cysts.—The commonest cysts of the kidney are the so-called retention cysts, which may occur in any variety of chronic nephrosis or nephritis, but are particularly frequent in the arteriolar variety of nephrosclerosis. Although these may originate from distention of the capsule of Bowman by accumulated secretion, it is believed that most of them represent dilated tubules whose outlet is constricted by connective tissue overgrowth. Grossly, such cysts are usually small and multiple, situated in the cortex rather than in the medulla. Occasionally, they may be so large as to occupy more than half the kidney. In any instance they are well defined and show a thin, transparent or translucent capsule and contain a limp, watery, colorless or pale yellow fluid.

The congenital cystadenoma of the kidney, often called the multiple cystic kidney, is believed to be of embryonal origin, although patients having

such kidneys may live to advanced years. The condition is usually bilateral and may be associated with similar cyst formation in the surface of the liver. The organs are enlarged, sometimes markedly so, weighing as much as 1000 grams or more. Grossly, the surface of the kidney is markedly lobulated by the projecting cysts. These have an average diameter of 6 to 10 mm. but may be much smaller or somewhat larger. The walls of the cysts are usually thin

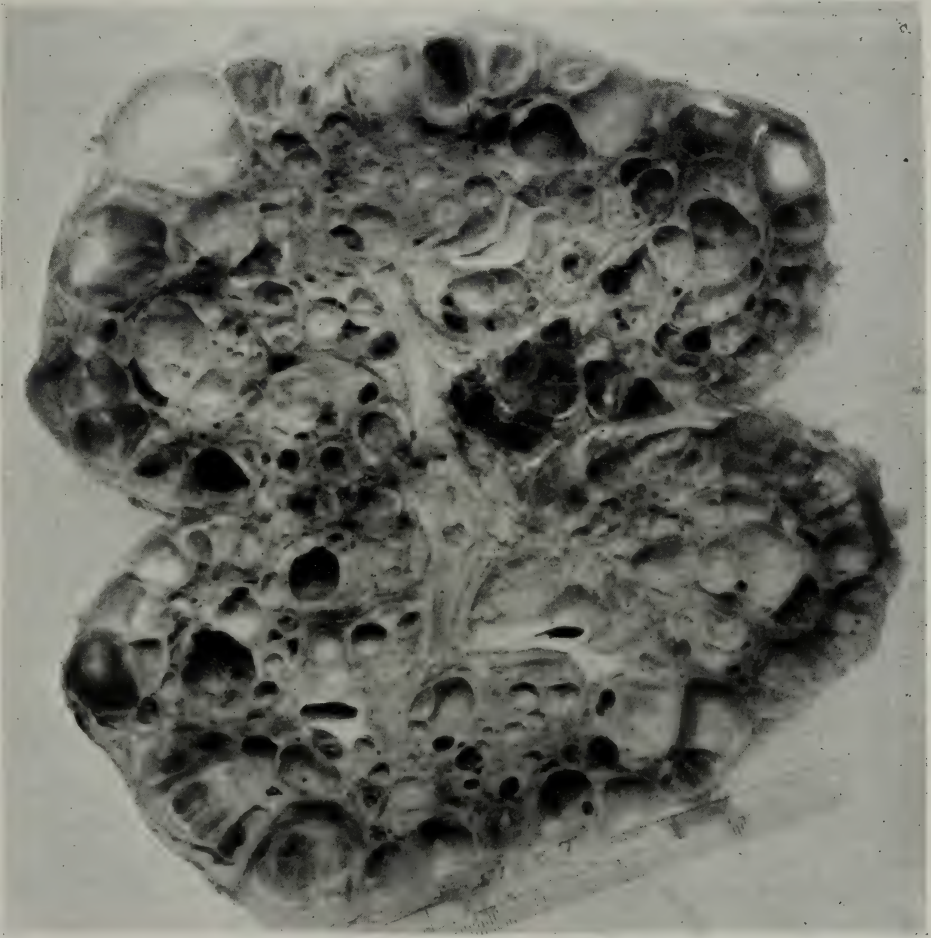


FIG. 336—Congenital cystic kidney in an adult.

and transparent. The cyst content may be clear, limpid, colorless, or pale yellow fluid, or a hyaline, firm, jelly-like mass either of light yellow or brown color. As a rule, no kidney substance can be seen with the naked eye. Microscopically, the cysts are found to have thin fibrous walls and are lined with cuboidal or flattened epithelium-like cells. Solidified cyst contents stain as a hyaline mass in the microscopic section. Kidney substance is found in the areas between the cysts. Although life may be sustained normally by such kidneys, nevertheless, most patients die with the symptoms and signs of

uremia. In two cases recently observed, one showed moderate hypertension and the other normal blood pressure.

Dermoid cysts of the kidney are occasionally observed. Rarely a cystic condition of the kidney is found in which the organ is replaced by a multilocular cyst with thick fibrous walls and containing clear limpid fluid. In such cases kidney substance is difficult to find either grossly or microscopically. The cyst is lined by epithelium but the mode of origin is unknown. The echinococcus cyst of the kidney is usually easily identified. For a complete study of cystic kidneys the reader is referred to Berner.

Parasites.—The most common animal parasite is the echinococcus cyst, which grows in the kidney usually as the simple cyst of this sort described in the chapter on liver and pancreas. Rupture into the pelvis may result in the discharge of hooklets in the urine. *Distomum hematobium* sometimes invades the renal pelvis. *Eustrongylus gigas*, observed in the kidneys of lower animals, occurs only rarely in man.

RENAL PELVIS AND URETER

Congenital Anomalies.—One or both ureters may be double, in which instance the renal pelvis usually shows greater or lesser division into two corresponding parts. If the orifice into the bladder be double, one occupies the usual position in the trigone and the other may empty into the colliculus, vas or seminal vesicle. Congenital narrowing or stricture of the ureter occurs particularly at the points where it is normally narrow, namely, at the outlet from the renal pelvis and at the entrance into the bladder (see Meyer). If sufficiently marked, such congenital stricture may lead to a congenital form of hydronephrosis. The ureters may show numerous variations in their course.

Circulatory Disturbances.—Passive hyperemia of ureter and of renal pelvis is not uncommon and shows distention of the veins sometimes associated with edema. Hemorrhage occurs in the course of acute inflammation, is one of the manifestations of severe anemia and of certain poisons, and may be due to erosion by calculi, or to the presence of tumors. The blood may coagulate in the ureter and be discharged, sometimes with colic, in the form of long narrow cast-like clots.

Inflammations.—Inflammation of the renal pelvis, pyelitis, and that of the ureter, ureteritis, are usually combined. Inflammation of these organs may be of the descending variety caused by organisms excreted through the kidney, or originating in infections of the kidney itself. The ascending form has been discussed in connection with the ascending variety of suppurative nephritis. In either case infection of ureter and pelvis appears to be favored by stagnation of the urine. Inflammations of the renal pelvis may be severe without distinct involvement of the kidney, but as a rule, ascent to the kidney occurs early and the condition becomes a pyelonephritis. The acute inflammations of these organs may be catarrhal in nature, due to bacterial invasion, the passage of drugs, such as cantharidin, and the presence of calculi. Purulent inflammations are due to the pyogenic cocci and to the colon bacillus. Rarely, such inflamma-

tions may be pseudomembranous in character and, particularly when calculi are present, the inflammation may be ulcerative in type. If obstruction to the outflow of urine does not occur before the onset of inflammation, the more severe inflammations almost invariably lead to obstruction with damming back of urine. Thus, the pelvis becomes filled with pus to constitute a pyonephrosis. As demonstrated by Hinmann and Lee-Brown, distention of the renal pelvis appears to permit backflow into the renal veins, so that there may be a more ready absorption of poisonous material from the pus and a more ready introduction of bacteria into the blood stream. Mild infection, or repeated acute attacks of inflammation, may produce a chronic pyelitis and ureteritis, with thickening of the mucosa and fibrosis of the underlying stroma. The epithelium may be thickened so as to produce numerous small polypi; in other instances numerous minute cysts are encountered, apparently arising from misplaced or aberrant epithelium in the wall of the ureter, pelvis and bladder (Stoerck). In the renal pelvis chronic inflammation and the presence of calculi may produce a thickening of the epithelial layers or a leucoplakia (see Richey). Of great importance is the fact that the healing of acute inflammations, or prolonged

chronic inflammations, may lead to single or multiple strictures of the ureters.

Tuberculosis of pelvis may be the result of a downward extension of tuberculosis from kidney, more especially the excretion form, or upward extension from tuberculosis of the bladder. The lesion of the pelvis has been described with tuberculosis of the kidney.

Hydronephrosis.—Damming back of urine into the renal pelvis with distention of the pelvis may be due to a wide variety of causes. Stricture of the urethra, congenital in origin, acquired as secondary to acute or chronic inflammation, due to kinks in the ureter from misplacement or floating kidney, accidental ligation during operation, the presence of calculi, of inflammations

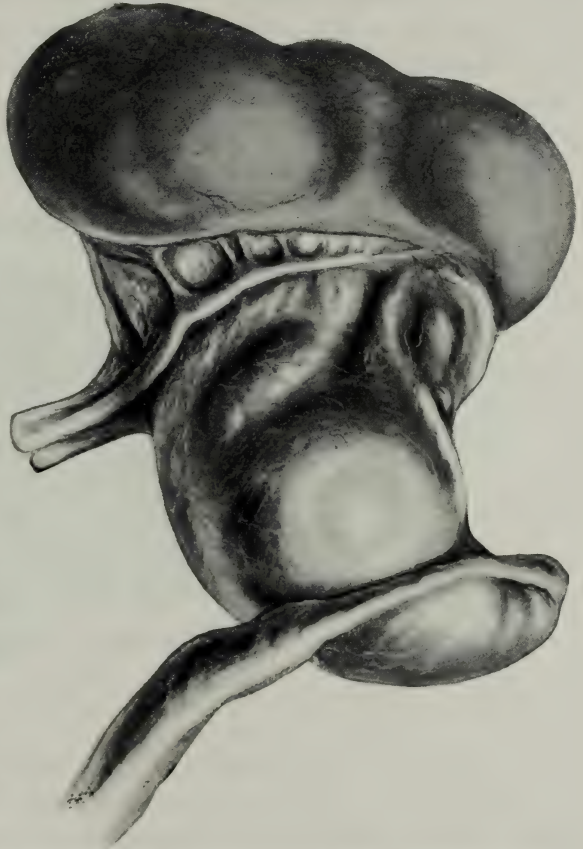


FIG. 337.—Marked hydronephrosis as a result of obstruction to the ureter by carcinoma of the uterus.

acute, chronic or tuberculous, and tumors involving the ureter and pelvis, may cause hydronephrosis. Other causes include compression by tumors in the abdominal cavity, megalocolon especially with stasis of intestinal content, tumors of the female genitalia, tumors of the rectum, and pregnancy. Obstruction of the outlet of the bladder because of inflammations, calculi within the bladder, enlarged prostate and stricture of the urethra may lead to bilateral hydronephrosis. As the result of these causes the hydronephrosis is of the so-called closed variety, or it may be partial. The explanation of open hydronephrosis is more difficult. The passage of urine through the ureters is due in large part to muscular activity, and it is highly probable that atony of the muscle as the result of involvement of the sympathetic or central nervous system, or of the muscle as the direct result of inflammation, may so interfere with ureteral movement of the urine as to cause dilatation of ureter and renal



FIG. 338—Cross section of kidney, the seat of hydronephrosis and multiple calculi.

pelvis (see Kutscherenko). In those cases where obstruction is in the urethra, the dilatation of ureter and pelvis may be in part reflex atony and in part reflux of urine into the ureters spoken of above.

The condition develops slowly, and varies in degree from a simple dilatation of the pelvis with little or no change in the kidney, to enormous dilatation of the pelvis with partial or complete disappearance of kidney substance. In the more severe cases the size of the kidney is considerably increased and the outer surface may be smooth or distinctly lobulated. The lobular projections correspond to the distention of the pelvis between the pyramids; the kidney substance being thicker at the pyramids is more resistant to the distention than is the cortical substance. In addition, Aschoff expresses the view that the outward projection may be contributed to in part by regeneration of epithelium and by fibrosis. The kidney substance itself is firm, pale and fibrous. The cut section is pale, usually retracts and bleeds very little. It is materially but irregularly thinned, the pyramids representing the thicker

parts. The pelvic wall is thick and fibrous. In the most advanced cases the kidney substance cannot be identified grossly and the entire mass is a large sac with dense fibrous wall which, in some instances, is calcified and even ossified.

Microscopically, the renal epithelium shows varying degrees of cloudy swelling, fatty degeneration and atrophy, going on finally to complete disappearance. There is fibrosis of the capsule of Bowman and of the glomerular tufts, with decrease in the size of the Malpighian bodies. The interstitial connective tissue shows a diffuse overgrowth, and in the most advanced cases entirely replaces the atrophic and absent epithelium and the fibrosed glomeruli. Although the latter at first appear as fibrous balls, later they lose their identity in a mass of fibrosis.

The studies of Ghoreyeb upon the circulation of the kidney, following ligation of the ureter, show that there may soon be distortion and compression of the blood vessels and cloudy swelling and fatty degeneration or even necrosis of the renal epithelium. After about ten days, interstitial fibrosis is well established and circulation permanently impaired. Keith and Snowden find, on the basis of experimental work, that hydronephrosis produces impairment of renal function with polyuria and albuminuria, decreased output of phenol-sulphonaphthalein, and moderate accumulation of total non-protein nitrogen in the blood. Clinically, the same phenomena may be observed. If bilateral, the condition may finally lead to uremia, often with marked acidosis.

Calculi.—The presence of calculi in the renal pelvis is spoken of as nephrolithiasis. Their composition has been discussed in the chapter on mineral infiltrates and concrements. In newborn infants it is not uncommon to find in the renal pelvis many small sand-like particles of urates, especially when “uric acid infarets” occur. Discharge of such “sand” in the urine is not uncommon in childhood and in later life. The particles may coalesce to form larger calculi. More especially in adults, calculi may be of considerable size. The smaller ones often have a rough, jagged surface but the larger ones are likely to be smooth. These are probably the result of accretion about a nidus of cells or mucus and many grow to fill part or all of the pelvis and adjoining calices. Calculi have a double relation to pelvic inflammations, in that inflammatory exudates may so disturb colloid-crystalloid relations as to lead to precipitation, and the presence of calculi may induce severe and even ulcerative inflammations. Pus or blood or both may occur in the urine. The passage of calculi through the ureter may produce ureteral colic. Large calculi in the pelvis, smaller calculi blocking the pelvic outlet or more commonly the ureteral outlet to the bladder, may be a cause of hydronephrosis.

Tumors.—Papilloma, covered by the transitional epithelium of the part, sometimes occurs in the renal pelvis but is extremely rare in the ureter. Myoma very rarely occurs in the ureter. Carcinoma of the renal pelvis, usually a papillary carcinoma made up of cells like those in the papilloma, constitutes a large, spongy, bleeding mass in the pelvis, may invade and destroy a large part of the kidney and may lead to distant metastases. Squamous cell carcinoma is extremely rare, and results either from prosoplasia of the lining

epithelium of the pelvis or of the cells during tumor growth (see Wells). The frequent association of calculi and carcinoma suggests irritation as a cause of the tumor, but in some instances the calculus may be a result of the presence of the tumor. Primary carcinoma of the ureter is also rare (Crance and Knickerbocker). Teratoid tumors sometimes occur in pelvis and ureter. Secondary tumors may be transported by blood or lymph vessels. Direct extension may

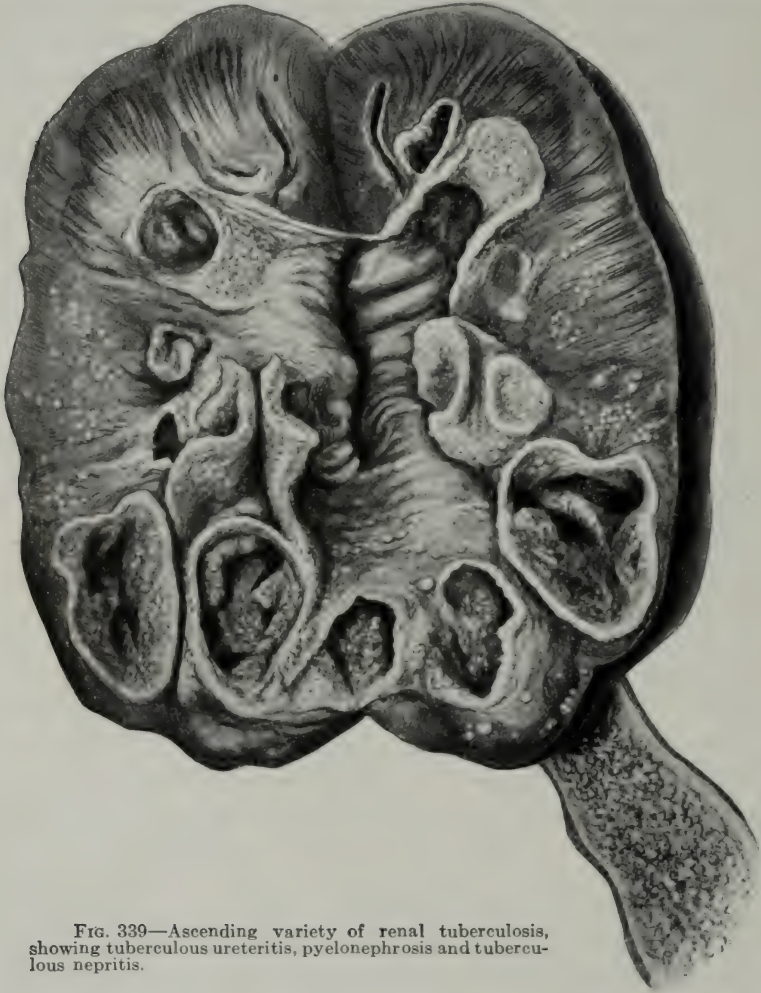


FIG. 339—Ascending variety of renal tuberculosis, showing tuberculous ureteritis, pyelonephrosis and tuberculous nephritis.

occur from malignant tumors of rectum, bladder and female genitalia, and from metastases in lymph nodes and in peritoneum. Hematuria is a frequent symptom. Hydronephrosis, sometimes with bloody fluid (hematonephrosis), is a common sequel of both primary and secondary tumors of the ureter.

THE URINARY BLADDER

Congenital Anomalies.—The most important of these is exstrophy of the bladder (see Von Geldern). This is due to failure of union of the lateral parts of the urogenital cleft. The bladder is an open sac communicating with the

lower abdominal wall, usually with red and swollen mucosa, which, if the patient reach adult life, may be the seat of extensive new gland formation. The condition is commoner in male than in female children. It is frequently associated with failure of closure not only of the anterior abdominal wall but also of the pubis, with anteriorly cleft penis or clitoris and often with complete inguinal hernia. The urachus may remain patent and the opening extend as far as the umbilicus. Infection may extend to the kidneys and become generalized.

Failure of septum formation may cause congenital vesicorectal or vesicovaginal fistula. The bladder is rarely absent. Septation of the bladder or multiple bladder has been reported. The urachus may remain completely or partially patent and in the latter condition sometimes becomes cystic. Cullen describes carcinoma, sarcoma, and tuberculosis of the urachus.

Circulatory Disturbances.—Passive hyperemia, more especially in women with misplacements of the bladder, may produce varices of the veins near the urethral outlet. Varices may also result from thrombosis of pelvic veins, especially in the aged. Hemorrhage is due to acute inflammations, calculi, tumors, parasites, direct trauma as by introduction of foreign bodies, or indirect trauma especially with fracture of the pelvis.

Inflammations.—Although it is probable that slight and evanescent acute catarrhal inflammation of the bladder may occur as the result of introduction of irritant chemicals and other substances, nevertheless, the important forms of acute cystitis are due to bacteria. Inflammation may result from the presence of foreign bodies, calculi, animal parasites, etc., but even under these circumstances bacteria are likely to play an important part as secondary invaders. The organisms concerned in cystitis are especially the bacillus coli communis, various forms of streptococci and staphylococci, bacillus typhosus and others. Apparently those which produce ammoniacal decomposition of the urine lead to more serious inflammations than those which do not. The most common route of infection is through the urethra, particularly from introduction of instruments, but apparently organisms are also carried into the bladder from the kidney, through the blood stream, and perhaps also through the lymphatic communications. In the vast majority of instances a most important predisposing cause of bladder inflammation is prolonged hindrance to the outflow of urine. Thus, inflammations and stricture of the urethra, enlargement of the prostate gland, especially the middle lobe, due either to inflammation, hyperplasia or tumor formation, cystocele, calculi in the bladder, tumors of the bladder, and paralysis of the bladder are likely to be complicated by cystitis. Sometimes the inflammation is local, as around the neck of the bladder in case of cystocele in women, or in and about acquired or congenital diverticula of the bladder.

Acute catarrhal cystitis exhibits slight or marked swelling of the mucosa, with hyperemia and sometimes adherent mucus upon the surface. Microscopically there is hyperemia, edema, cloudy swelling of the epithelium with desquamation and slight infiltration of lymphoid cells and leucocytes. The urine contains desquamated epithelium, lymphoid cells and leucocytes and

stringy mucus in the form of cylindroids. It may or may not be alkaline, depending upon the type of organism concerned.

Acute purulent cystitis shows pronounced hyperemia and swelling of the mucosa and usually a covering of purulent material. Abscesses in the mucosa and ulceration are not uncommon. Microscopically, there are found hyperemia, edema and diffuse infiltration of inflammatory cells, particularly polymorphonuclear leucocytes, associated with necrosis, desquamation and ulceration of the epithelium. As time goes on the process may involve the deeper structures of the bladder to produce an acute phlegmonous cystitis. This may be followed by penetration of the suppurative process into the surrounding tissues, especially where there are diverticula of the bladder. The bladder wall may become so soft as to be ruptured by a catheter or other instrument. We have observed one case in which penetration through a diverticulum resulted in extensive paraecystic inflammation and death from pyemia. Pene-

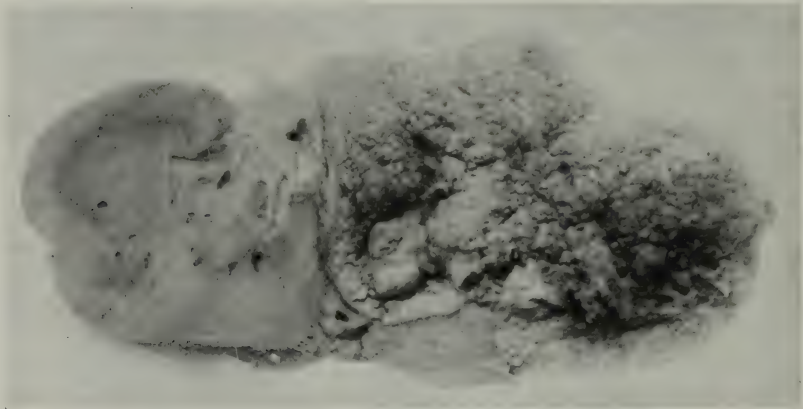


FIG. 340—Papillary carcinoma of the renal pelvis infiltrating the kidney.

tration into the peritoneum may lead to local or generalized peritonitis. Since the pyogenic organisms can and do produce ammonia, the urine in purulent cystitis is likely to be alkaline. It contains desquamated epithelium and large numbers of leucocytes and pus cells, which may be so abundant as to form a large bulk of urinary sediment. The alkalinity of the urine may lead to such swelling in the cells that they become indistinguishable. Bacteria are usually present in large numbers. Hemorrhage is distinctly more common than in the catarrhal form. The precipitation of phosphates and carbonates in the urine may produce a certain amount of encrustation of the bladder walls.

Acute fibrinous or fibrinopurulent cystitis usually represents an extremely severe local infection, an infection brought by the blood stream, or an infection complicating corrosive chemical action. The signs of inflammation are pronounced, and in addition there is likely to be not only extensive necrosis and greater or less degree of hemorrhage, but also a deposition of a fibrinous or fibrinopurulent mass, especially along the crests of the contracted muscle bands. The necrotic part and the fibrin membrane are often of dark brown

color and the lining of the bladder may be encrusted as in the purulent form (see Carson).

Chronic cystitis may be the sequence of one or repeated attacks of any of the above forms, but is more likely to follow the catarrhal than the purulent or fibrinous variety. Usually the entire bladder wall is thickened and fibrosed but occasionally atrophic forms may be observed. Because of the obstruction which leads to inflammation or which is secondary to prolonged inflammation, there is likely to be hypertrophy of the muscle. Associated with the hypertrophy there is almost always interstitial fibrosis between the muscle bands. The mucosa may show a simple thickening of catarrhal character with fibrosis and infiltration of lymphoid cells, or may be the seat of chronic ulceration. Sometimes the lining epithelium becomes transformed from the intermediate form to a definite stratified squamous epithelium, a condition spoken of under the general heading of prosoplasia. More uncommon varieties of chronic cystitis include cystitis cystica, referred to in connection with diseases of the ureter, a nodular variety in which the mucosa is thrown up into nodules, and a polypoid variety in which polypoid masses project into the bladder. The last is not uncommon in connection with infestations of the bladder by distomum hematobium. In young people who have calculi in the bladder, the lining epithelium may not only become squamous in character but there may be considerable keratinization with the development of a leucoplakia.

Malakoplakia, a very rare condition, is characterized by the appearance on the lining of the bladder of numerous slightly projecting, gray or yellowish-gray nodules, semitransparent, with an opaque depressed or necrotic center and a surrounding zone of hyperemia. Although in a majority of cases, according to MacDonald and Sewell, the bacillus coli communis is found, it is not certain that this is the direct cause of the condition. The nodules are of inflammatory or granulomatous character, made up of leucocytes, lymphoid cells, fibroblasts, connective tissue cells and peculiar large cells, the so-called malakoplakia cells. These are apparently phagocytic and contain debris of corpuscles, leucocytes and bacteria. Within the phagocytes and also free in the tissues are to be found the so-called Michaelis-Gutmann bodies, the nature of which is not known, although it is probable that they represent necrotic cells of some sort. The same process may affect ureters, renal pelvis, and occur as nodules within the kidney.

Tuberculosis.—Although in generalized miliary tuberculosis, miliary tubercles may be observed in the bladder wall, and although occasionally tuberculosis may extend from the prostate and seminal vesicles in massive form into the bladder, nevertheless, the most important form clinically and pathologically is that which originates as miliary tuberculosis around the orifice of the ureters, apparently as the result of transmission of bacteria from the upper urinary tract into the bladder. Tubercles may form more widely in the trigone and even further along the posterior bladder wall. They are likely to break down and produce small, shallow, caseous ulcers which may fuse to form large ulcerated areas. The surrounding mucosa is usually distinctly

hyperemic, but the bladder as a whole is the seat only of a mild catarrhal cystitis. The margins of larger ulcers may show numerous daughter tubercles. In uncomplicated cases the urine is clear and acid, occasionally blood tinged, but when secondary infection supervenes, the urine may take on all the characters of any of the acute forms of cystitis and the bladder itself may show widespread secondary inflammation.

Syphilis.—In the secondary stages of syphilis mucous patches similar to those observed in other mucous membranes may occur. Gumma is not common but is seen more frequently in the trigone than in other parts of the bladder.



FIG. 341.—Extensive tuberculosis of the bladder, showing the most marked involvement near the urethral orifice.

Alterations of Size and Form.—Dilatation of the bladder occurs as the result either of paralysis of the muscle or as the result of obstruction to the urethral orifice. If the obstruction be of short duration, as is observed in those spasmodic forms of retention of urine which occur after operations in the region of the pelvis, recovery may be rapid and complete. If the obstruction be prolonged, as in enlarged prostate, a hypertrophy accompanies the dilatation. In uncomplicated dilatation the amount of urine may be very large, and sometimes the bladder is palpated as high as the umbilicus.

Localized dilatations or diverticula of the bladder may be single or multiple, and usually are observed in the posterior wall about the orifices of the ureter or near the insertion of the urachus. Two varieties are distinguishable, although sometimes with difficulty. The true diverticulum is usually of con-

genital origin and all the coats of the wall of the bladder, somewhat attenuated, take part in the dilatation. False diverticula, which in our experience are much more common, appear as dilated areas pouching out between bundles of muscle, usually in a hypertrophic bladder. These are presumably due to increased pressure within the bladder, so that at the point where the musculature is thinner than elsewhere, the outpouching occurs. It is at least conceivable that in some instances there is a congenital weakness of muscle in these parts. Inasmuch as urine is likely to stagnate in the diverticula they become favored parts for inflammation, with a possibility on the one hand of extension through the wall or rupture of the diverticula, or on the other hand, extension of the inflammation throughout the bladder. Diverticula also appear to be favorable points for the deposition of calculi.

The bladder may rarely take part in hernias, but the most important malposition of the bladder is that due to relaxation of the pelvic floor in women. The support of the posterior wall of the bladder, furnished by proper position of uterus and vagina, may thus give way so that the bladder is misplaced posteriorly and bulges into the vagina in the form of the so-called cystocele. The urine may stagnate in the outpouched portion of the bladder and inflammation ensue, but it is rare that such severe inflammation is observed as is true in diverticula. Prolapse of the uterus may cause inversion of the trigone, which may result in kinking of the ureters as they enter the bladder. The upper part of the bladder may pouch downward into the cavity of the bladder, the so-called inversion, or it may even project through the urethral orifice, constituting prolapse of the bladder.

Hypertrophy of the bladder is practically always accompanied by a variable degree of dilatation. It may be caused by any of the conditions mentioned in discussing the etiology of inflammation, which produce prolonged obstruction to outflow of urine. The bladder wall is variably thickened and fibrosed. The outstanding feature is the fact that the muscle undergoes hypertrophy in interlacing bundles or bands, which constitute the so-called trabeculae of the bladder, producing the condition spoken of as trabeculation.

Rupture of the bladder, or perforation, occurs as the result of fractures of the pelvis whereby fragments of bone penetrate the organ. In labor, prolonged pressure of the fetal head upon the bladder and vagina may cause necrosis of the tissue and subsequent perforation. Instrumentation may produce perforation, more especially, however, when the bladder is the seat of inflammation or necrosis. Perforation may also be caused by wounds of bullets, knives, etc. Considerable external pressure upon a distended bladder may produce rupture. Malignant tumors of the bladder, vagina, uterus, and other neighboring structures may lead to perforation of the bladder. Depending upon the site of perforation, urine may enter the peritoneum or infiltrate the pelvic tissues. Following the latter, the infiltration may extend to the skin of the lower abdomen and pelvis. As the result of birth injuries or the presence of malignant tumors, ruptures may lead to the establishment of fistulae between neighboring organs such as vesicovaginal, vesicorectal and vesicouterine fistulae.

Calculi.—These occur principally in males in later middle life but are not rare in women and children. They vary in size from a fraction of a millimeter to several centimeters. The larger calculi are usually single and if multiple may be faceted. The smaller ones may be so numerous as to justify the term sand for the very small ones or gravel for slightly larger ones. Calculi may be primary in the bladder or may pass into the bladder after originating in renal pelvis or ureter. Inflammations of the bladder may be a cause or a sequence of calculus formation. Aschoff divides calculi into those of non-inflammatory and of inflammatory origin.

Of the primary calculi of non-inflammatory origin, the urate calculus is probably the most important. It is made up principally of ammonium urate, mixed also with sodium urate and sometimes uric acid. Such calculi occur especially where there is undue excretion of uric acid as in leucemias, the puerperium, lobar pneumonia, rheumatic fever, etc. The calculus is usually small, firm, angular, yellowish-brown, and in multiple form usually constitutes gravel or sand. The oxalate calculi, apparently the most common urinary calculi (Kahn), usually originate in the renal pelvis and are small, hard, of irregular contour and of light or dark brown color. The cystine calculi are unusual; they are small, smooth, round, translucent, waxy, white or pale yellow, sometimes lamellated, bodies. The xanthine calculi are smooth and of brownish-red color. Phosphate calculi, round with slightly granular surface and chalky character, are more often secondary than primary.

Such primary non-inflammatory calculi may be discharged with the urine, but if they remain they may act as physical foci for further precipitation and show secondary encrustations in the form of lamellæ. In a general way if the urine be acid, the encrustation is of urates, if neutral, of oxalates, and if alkaline, of phosphates. The last occurs principally after bladder infection is established.

Calculi of inflammatory origin may be in the form of non-inflammatory calculi with secondary lamellation, or may be primary, in which case they are usually due to precipitation from ammoniacal alkaline urine of ammonium magnesium phosphate, calcium phosphate, calcium oxalate and ammonium urate (Wells).

The centra for calculus deposition, most especially those of inflammatory nature, include foreign bodies introduced from without, desquamated cells and tissue masses, parasites and their ova, bacteria, mucus, etc., but sometimes, even although organic matter may constitute a part of the calculus, a nidus cannot be found.

Foreign Bodies and Parasites.—The foreign bodies include those introduced through the urethra such as instruments or their fragments, and a wide variety of substances such as needles, pins, pencils, etc., introduced as the result of sexual perversion or other mental disturbance, mineral encrustation especially due to inflammation, epithelial cells, tissue masses especially from tumors, solid materials gaining access through fistulæ. The parasites include distomum hematobium, the ova of which are often found in the urine, echinococcus, filaria bancrofti. Oxyuris vermicularis, trichomonas and similar organ-

isms may gain access to the urinary bladder presumably through the urethra.

Tumors.—The benign tumors of rare occurrence include fibroma, adenoma, myxoma, hemangioma, leiomyoma, rhabdomyoma, and mixtures of these. Occasionally, also dermoid cysts and other types of embryonal growth have been encountered, which, as they are usually situated in or near the trigone, are believed to originate from misplaced remnants of the Wolffian duct. The most common benign tumor and probably the commonest primary tumor of the bladder is the papilloma. This usually occurs as a pedunculated form, which consists of an outgrowth from the wall of the bladder of vascularized connective tissue arranged in multiple papillæ, all covered by stratified intermediate epithelium. Much less frequent is a sessile form in which the base spreads fairly widely over the bladder wall. Grossly, the papilloma is a pale red, shaggy, pedunculated, or cauliflower-like growth, which bleeds very readily. Microscopically, the supporting connective tissue is found as of delicate adult type with rich vascularization. The epithelium in the majority of cases is practically identical with that lining the bladder, but minor changes in conformation of the cells, such as elongation or flattening, even with keratinization, may be observed. The papilloma has a striking disposition to recur, after removal and may also undergo malignant change. According to Buerger, the possibilities include recurrence of papilloma, the development of a more or less diffuse papillomatosis of the bladder lining, the development of a carcinoma, and the possibility that when diffuse papillomatosis occurs any one of the constituent papillomata may become malignant.

Of the malignant tumors the carcinoma is by far the most frequent. Although focal forms of primary carcinoma of simplex type, more diffuse infiltrating carcinoma of similar character, and also squamous epithelioma, are occasionally observed, the most frequent form is the papillary carcinoma which may originate as such or be the further development of a papilloma. The papillary carcinoma is a shaggy cauliflower-like mass which bleeds freely and upon examination shows definite invasion of the bladder walls by epithelium. On microscopic examination papillary arrangement is less sharply defined and the number of fibrous tissue trabeculæ is relatively less than in the papilloma. Buerger's studies indicate that the significant changes in the epithelium, which differentiate the papillary carcinoma from the papilloma, include considerable irregularity in size and shape of the cells, nuclei which are rich in chromatin and of irregular shape, typical and atypical mitotic figures and multinucleated cells. When tissue is favorably taken, epithelial invasion can be readily made out.

Primary sarcoma is very rare but includes a nodular and an infiltrating form, which microscopically may prove to be lymphosarcoma, round cell sarcoma, spindle cell sarcoma or indeed any form of the more highly differentiated sarcomas.

Secondary carcinoma of the bladder is most commonly an extension from carcinoma of the cervix uteri, but also may be from prostate and from rectum. It is only rarely that carcinoma in other situations shows secondary deposits in



FIG. 342—Cross section of penis, showing stricture of membranous urethra, dilatation of the proximal portion and false passage extensive distally.

the bladder. Sarcoma may extend from any of the pelvic viscera and occasionally the bladder is involved in melanosarcomatosis.

Cysts of the bladder include the dermoid cysts, the echinococcus cysts and rarely small serous cysts in the posterior inferior wall. The last occur particularly in men and are believed to represent cystic dilatation of remnants of Müller's duct.

THE URETHRA

Congenital Anomalies are distinctly more frequent in the male than in the female urethra. They include atresias of various degrees, folds of various kinds, double urethra, epispadias, hypospadias, and diverticula. In epispadias the urethra opens on the upper surface of the glans or of the penis and in hypospadias on the lower surface.

Inflammations.—Although acute urethritis may be due to various organisms, more especially in the female by introduction from vagina and vulva, or the result of infection of wounds, the most common is that due to the gonococcus introduced by sexual contact. In the male, gonorrhea is a disease primarily of the anterior urethra, but in females it is more likely to attack the cervix uteri. Gonorrhea ordinarily occurs as an acute anterior purulent urethritis, which affects the epithelium and underlying connective tissue, and occurs about nine days after the infection. There are hyperemia, edema, leucocyte infiltration, epithelial desquamation, and sometimes hemorrhage. Microscopic examination of the pus, usually large in amount, viscid, deep yellow or greenish-yellow in color, shows numerous pus cells, desquamated epithelium, gonococci both intra- and extracellular, and sometimes other organisms. The process may be limited to the anterior urethra but may extend to the posterior portion, to the epididymis, seminal vesicles, prostate, bladder and by so-called metastasis may involve joints, tendon sheaths, endocardium and other

structures. In the female it may affect endometrium, Fallopian tubes and pelvic peritoneum. Another surface which is especially susceptible is the conjunctiva, most commonly affected at birth but also affected in adult life by manual transfer of the organisms from the urethra. Opacities of the cornea, iritis, iridocyclitis and panophthalmitis may result.

Chronic urethritis is usually gonorrheal and affects especially the posterior urethra as a chronic catarrhal process, sometimes associated with metaplasia to squamous epithelium, a leucoplakia, and ulceration.

Stricture.—The contraction of scar tissue following acute or chronic inflammations (usually gonorrheal) or wounds, leads to narrowing of the urethral lumen, sometimes completely stopping the flow of urine. The urethra may dilate behind the stricture. The obstruction to urinary outflow may lead to dilatation and hypertrophy of the bladder, dilatation of the ureters and renal pelvis and to inflammations in these situations. Ulceration behind the stricture or rupture by instruments may lead to widespread urinary infiltration of the external genitalia, perineum and adjacent skin of thighs and lower abdomen, usually followed by infection of the infiltrated parts.

Infectious Granulomata.—Chancre and gumma may affect the urethra. Tuberculosis is usually an extension from a tuberculous prostate or from a lupus of the vulva.

Tumors.—Benign tumors such as papilloma, adenoma, fibroma, etc., are rarely encountered. Fairly common in women is the urethral caruncle, which is included here for convenience. That it is a tumor is doubtful. It is situated at or near the internal urethral orifice and is usually a more or less pedunculated mass a few millimeters in diameter. Histologically, it is covered by urethral epithelium, and although occasionally of granulomatous character, as a rule is made up either of highly vascularized connective tissue, or, as is more common in our experience, is telangiectatic in structure.

Primary carcinoma is usually in the form of squamous epithelioma, or rarely adenocarcinoma, probably originating from the glands of Cowper. Sarcoma, including melanoma, lymphosarcoma, spindle cell sarcoma and other forms, is extremely rare. Secondary tumors are also rare.

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CHAPTER XIX

THE GENITAL SYSTEM

MALE GENITALIA.

PENIS.

SCROTUM.

TESTIS AND EPIDIDYMIS.

SEMINAL VESICLES.

PROSTATE.

FEMALE GENITALIA.

VULVA.

VAGINA.

UTERUS.

PLACENTA.

FALLOPIAN TUBES.

OVARY.

THE BREAST.

MALE GENITALIA

Congenital Anomalies.—The penis may be absent, the urethra opening into perineum or rectum. The organ may be unusually small (micropenis) or large (megaloopenis). It may be cleft, double, or may be adherent to the scrotum. Epispadias and hypospadias have been mentioned in discussing the urethra. "The foreskin may be absent, incompletely developed, redundant, or adherent to the glans; the preputial orifice may be absent or extremely small; the frenum may be abnormally short" (White and Martin). Phimosis, a condition in which the preputial orifice is too small to permit retraction of the prepuce is a common congenital defect.

The anomalies of the testes include those of number, size and position. It is doubtful that supernumerary testes, or polyorchism, occurs. Anorchism may be unilateral or bilateral, associated usually with absence of the epididymis and scrotal vas. Fusion or synorchism is reported in the fetus. Testes vary in size under normal circumstances. Congenital aplasia or hypoplasia is referred to as micro-orchism and if severe may be associated with the "eunuchoid" state, in which feminine secondary sex characters are exhibited. Alterations in position include ectopy, or position outside the normal sites, as in the groin or perineum, inversion or retroversion in the scrotum, but the most important is undescended testis. This last is due to incomplete descent of the testis through the inguinal canal to the scrotum. If unilateral it is usually called undescended testis, but if bilateral the term cryptorchism or cryptorchidism is employed. The organ remains usually in the inguinal canal but may not leave the abdomen. The descent usually takes place before puberty, but if this fail the testis often remains small and hypoplastic. Although its function may be quite normal it is susceptible to inflammation following traumatic injury, and is more likely to be the seat of malignant tumors than if normally situated. Hernia is a common accompaniment of undescended testis.

Hermaphroditism.—True hermaphroditism signifies the presence of developed functioning testis and ovary in one individual. It is extremely doubtful that it occurs in man. The genital glands may rarely show both ovarian and testicular tissue, the so-called ovotestes, but one sex predominates. Malformations of genitalia give rise to the condition called pseudohermaphroditism in which the external genitalia may resemble one sex and the general body make up be that of the other, the latter being determined by the character of the sex glands. In males undescended testes and bifid scrotum may look like labia majora, which when associated with aplastic penis, with perineal hypospadias and sometimes a perineal pouch, give the appearance of female genitalia. Females may exhibit a large clitoris, absence of, or small vagina (with small uterus and ovaries), thus giving the external appearance of male genitalia. Confusing cases occasionally occur in which it is impossible without microscopical examination of the sex glands to determine the sex of the individual.

THE PENIS

Phimosis.—Congenital phimosis has been referred to. Acquired phimosis may result from acute inflammations with so much swelling that the foreskin cannot be retracted, or from cicatricial contraction of the preputial orifice. *Paraphimosis*, a condition in which a retracted prepuce cannot be brought forward by ordinary means, results from inflammatory or edematous swelling of a retracted foreskin, from swelling which produces a rolling back of the foreskin, or from forcible retraction of a phimotic foreskin. The frenum may be short congenitally or as the result of cicatricial contraction, and this may interfere with erection and coitus.

Circulatory Disturbances.—Marked passive hyperemia and edema of the glans accompany paraphimosis. The penis may be the seat of passive hyperemia and edema as the result of general diseases such as myocardial insufficiency. Local edema may result from blocking of lymphatics by scar tissue or by filaria bancrofti. Thrombosis of veins as the result of wounds, or sometimes as the result of leucemia, may lead to priapism.

Inflammations.—The more common acute inflammations include balanitis or inflammation of the glans, balanoposthitis in which the inflammation involves also the prepuce, chancroid and herpes. Balanitis and balanoposthitis are favored by redundant or phimotic prepuce with accumulation of the secretion of Tyson's glands, desquamated epithelium and urine. Although smegma bacilli may be abundant, the exciting organisms are usually colon



FIG. 343.—Balanitis, from Genito-Urinary Surgery, by Martin, Thomas and Moorhead.

bacilli or pyogenic cocci. The inflammation may be slight, but may become ulcerative, and in the presence of phimosis may become gangrenous. Involvement of the inguinal lymph nodes is not common. Balanitis may also be due to irritant urethral discharges, particularly of gonorrhea. Herpes progenitalis is characterized by the abrupt appearance, usually in the coronary sulcus, of vesicles with a slightly inflamed base. The surface of the vesicles quickly macerates, leaving small discrete or confluent ulcers. The lesion may be due to balanitis, to immoderate coitus, to contact with irritating discharges from vagina or uterus, or to some of the general causes of herpes.

Acute inflammations may extend into and produce acute lesions of the substance of the penis. The condylomata which may follow prolonged superficial inflammations will be discussed with tumors. Leucoplakia is sometimes observed.

Chancroid or soft chancre is defined admirably by Keyes as "a specific, local, contagious, auto-infectious venereal ulcer." It occurs in single or multiple



FIG. 344—Multiple chancroids of coronary sulcus, from Genito-Urinary Surgery, by Martin, Thomas and Moorhead.

form, usually in the coronary sulcus near the frenum, and in females about the introitus, but may spread to neighboring regions or may be primary in other situations. It is caused by the Ducrey-Unna bacillus which in the hands of Davis and others has fulfilled the postulates of Koch. It is a gram-negative, short, relatively thick bacterium with rounded ends and a narrow median portion which gives the "dumb-bell" shape. The pus from the lesions shows intra- and more especially extracellular organisms, single, in pairs, and in short chains, grouped in parallel or fan-like rows. It grows readily in the serum of coagulated rabbit blood (Teague and Deibert) and shows long chains, often with involution forms.

The lesion appears after a variable but short incubation period, which in auto-inoculation lesions is about twenty-four hours. An interruption of surface continuity is essential for the implantation of the causative organism. It is primarily a seropurulent lesion in and immediately under the epiderm. The surface sloughs in a few hours leaving the ulcer. As usually seen the ulcer is rounded, has soft, sharply defined, sometimes undermined edges, a surrounding zone of hyperemia and a necrotic, smooth or irregular base covered with pus.

Histologically, the ulcer shows the necrotic base infiltrated with leucocytes. The surrounding area shows a similar infiltration combined with plasma cells, lymphoid and endothelial cells. In addition to the dilatation of the blood vessels there is an acute peri- and endovasculitis (Demanche). The organisms can be demonstrated in the sections.

Secondary infections usually occur, and organisms other than the Ducrey-Unna bacillus may predominate. This may produce a spreading destructive phagedenic ulcer or even gangrene. Increasing cleanliness and hygienic care of the population has apparently led to a recedtion in severity of the infected chancroid, and it has been suggested that a relative immunity is gradually developing. Although lymphangitis is not common, suppuration of the inguinal lymph nodes is frequent and rarely the iliac nodes may be involved. The inguinal "bubo," if not incised, often breaks through the skin of the groin to produce purulent deep ulcers which may become gangrenous.

Infection with syphilis may occur at the same time as that with chaneroid. The latter lesion with its shorter incubation period appears first and is followed by the indurated inactive ulcer of hard chancre. This combination is often called mixed chancre.

Chronic inflammations of the penis with deposition of fibrous tissue are sometimes observed in older men, and usually cannot be ascribed to definite cause other than gouty and rheumatic diathesis. The fibrosis appears especially in the corpora cavernosa and tunica albuginea testis, as small or extensive nodules which may be calcified or even ossified.

Infectious Granulomata.—The primary lesion of syphilis, the chancre or hard chancre, is seen usually upon the glans, near the frenum or upon the prepuce. Its character has been described in the chapter on infectious granulomata. In the secondary stage mucous patches or flat condylomata may be observed upon glans, prepuce, or skin near the scrotum. In late syphilis gumma may occur in the glans and the corpora cavernosa; the scars may produce much deformity. Tuberculosis may involve the penis following the tuberculous urethritis of extensive urogenital tuberculosis. Rarely tuberculous infection occurs by coitus, or by sputum in perversion or in religious circumcision. Lupus is also rare. Granuloma inguinale described in the chapter on infectious granulomata may affect the skin of the penis. Actinomycosis and leprosy are rare.

Tumors.—Benign tumors include lipoma, adenoma, angioma and papilloma. The papillomata include the common wart and also the acuminate condyloma, which latter although not necessarily of venereal origin is sometimes called venereal wart. The acuminate condyloma, sometimes single but usually multiple, occurs in the coronary sulcus, but may be seen upon glans, foreskin or even in the urethra. The cauliflower like mass may be sessile or pedunculated, shows numerous villi covered by stratified squamous epithelium, is usually pink in color and bathed in a thin mucoserous or seropurulent discharge. As noted in the chapter on tumors, such growths may be regarded as either inflammatory hyperplasias or as tumors. They follow irritations of

the part resulting from the various forms of balanoposthitis, urethritis or uncleanness. Cutaneous horns may occur.

Although sarcoma, usually with rapid regional metastasis, may occur in the penis (Joelson), the most important malignant tumor is the squamous epithelioma. This originates most frequently on the glans and somewhat less so on the prepuce (Barringer and Dean), and in contrast to the acuminated condyloma is not often primary in the coronary sulcus. It usually occurs after fifty years of age but cases in much earlier life have been reported. It is likely to have a history of wart, prolonged balanitis or phimosis. The commoner form grossly is a destructive infiltrative papillary or cauliflower-like tumor, but there is also a form which occurs as an indurated sluggish ulcer. It invades the penile structures slowly, shows tardy metastasis to the inguinal lymph nodes and is only rarely widely disseminated. Inflammatory reaction and keratinization of epithelium are usually pronounced in the histologic section.



FIG. 345.—Carcinoma of penis with early lymphatic involvement, from *Genito-Urinary Surgery*, by Martin, Thomas and Moorhead.

Owing to the infection of the superficial tumor, inflammatory enlargement of the inguinal lymph nodes is common and should not be confused with metastasis.

Cysts about the raphe are usually congenital epidermoid cysts or dermoid cysts. Cystic dilatations of sebaceous glands or of Tyson's glands are sometimes observed.

Concrements in the preputial sac are either waxy masses of inspissated smegma, sometimes infiltrated with phosphates, or calculi made up of urinary salts which may be primary or secondary from small calculi originating in bladder or renal pelvis.

Urethra.—Lesions of the urethra including gonorrhea have been discussed in the chapter on urinary system.

THE SCROTUM

The scrotum is subject to a wide variety of skin diseases of which eczema and dermatitis venenata may lead to great swelling. Intertrigo is a mild dermatitis resulting from moisture and uncleanness in obese individuals or

in children. Pityriasis is sometimes severe. Pediculosis is due to pediculus pubis which differs slightly from the body louse. Inflammations of all kinds, originating from wounds, from urinary infiltrations, from extensions of neighboring inflammation, are likely to show marked edema. Phlegmon, cellulitis or abscess are most often the result of urinary infiltration from ruptured urethra.

Elephantiasis is a prolonged lymph stasis accompanied by chronic lymphangitis and fibrosis of the interstitial tissue. Moderate grades may occur following cicatricial closure of lymphatics or excision of inguinal lymph nodes. The most severe grades are due to occlusion of the lymphatics by the adult filaria bancrofti, and the associated chronic inflammatory change which the parasite sets up. The microfilaria may be found in the circulating blood. Mosquitoes take up the microfilaria and serve as intermediate hosts for the

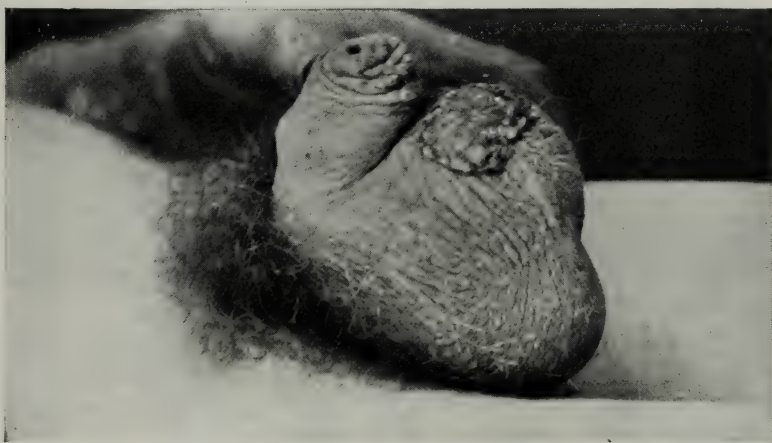


FIG. 346—Epithelioma of scrotum, from *Genito-Urinary Surgery*, by Martin, Thomas and Moorhead.

development of the larval prefilarial phases, which are transmitted to a new human host by the mosquito bite. The scrotum may attain enormous size; rupture of the dilated lymphatics into the urinary tract may cause chyluria or hematochyluria.

Tumors.—Numerous benign tumors such as affect the skin may occur. Sebaceous cysts, epidermoid and dermoid cysts, and small blood cysts may also occur. The most important tumor is the epithelioma of the scrotum or “chimney-sweep’s cancer” which is a squamous epithelioma appearing grossly either as a papillary or ulcerative form. It is seen also in workers in coal tar products. It grows slowly and metastasizes late.

TESTIS AND EPIDIDYMIS

Lesions of Tunica Vaginalis.—Only the commoner lesions of this sac will be considered. Acute inflammations may be of traumatic origin, most commonly result from extensions from testis and epididymis, or may rarely be blood borne as in a septicemia. The exudate may be serous, serofibrinous or

purulent. Tuberculous or syphilitic involvement is usually by extension from testis or epididymis. Chronic inflammations may represent a continuation or sequel of acute lesions. There may be considerable accumulation of fluid, or adhesions, or both with the formation of loculi.

Hydrocele is the accumulation of fluid in the tunica vaginalis. In the congenital form the fluid is peritoneal and due to failure of closure of the funicular process. In the infantile form the process is closed and fluid is found both in the tunica and in the process. Congenital and infantile forms are often accompanied by hernia. The lesion found in adults is a gradual, or less often rapid, accumulation of fluid, usually 100 to 300 cc. in amount but sometimes more than two liters. The cause is unknown but it is more common in middle life and in the tropics. The fluid is clear, colorless, slightly viscid and contains from 6 to 10 per cent. of solids, including proteins, fibrin, salts and sometimes grossly visible cholesterol. It contains desquamated epithelium, leucocytes and sometimes erythrocytes and also bacteria. Wells suggests that its character simulates both exudate and transudate. Usually repeated drainage by puncture leads to a character more closely resembling exudate.

Hematocoele indicates the presence of blood in the tunica vaginalis. It may be due to trauma, to hemorrhagic diseases or secondary to hydrocele. *Chylocele* occurs in connection with elephantiasis in which lymphatics rupture into the tunica. *Spermatocele* is a cystic dilatation of ducts in the head of the epididymis or in the rete testis. It may rupture into the tunica vaginalis to produce spermatic hydrocele.

Varicocele is included here for convenience. It is a varicose dilatation of the veins of the pampiniform plexus. It sometimes is due to interference with drainage, as by pressure of intra-abdominal tumors, but more often occurs without known cause. It is a condition extremely common in young men, affecting almost exclusively the left side. It apparently has little or no connection with general venous stasis, and rarely has any significance.

Hernia has been discussed in the section on peritoneum in the chapter on alimentary system.

Lesions of Testis and Epididymis.—These organs may share in moderate degree in general passive hyperemia. Hemorrhage may result from trauma, hemorrhagic disease or torsion of the spermatic cord. Fatty degeneration of epithelium may be seen in atrophy and in chronic inflammations. Iron-bearing pigment is observed in severe anemias, hemochromatosis and in the atrophy of old age. Hyalin occurs in various atrophic and fibrotic lesions of the testis; amyloid may be observed in association with amyloid of other viscera.

Acute Inflammations.—Both acute orchitis and epididymitis are most commonly caused by extensions from the urinary tract. Therefore the epididymis is affected first, more severely and sometimes solely. The most frequent cause is gonorrhea, which may first affect seminal vesicles and vas, but often attacks the epididymis directly. Rarely the testis is attacked independently of the epididymis. The lesion begins as a rule in the tail of the epididymis, extends to involve the whole organ, becomes associated with a serous or

serofibrinous vaginalitis and may involve, presumably by lymphatic extension rather than by continuity, the neighboring parts of the testis. Suppuration begins in the tubules and extends to the interstitial tissues, where following a preliminary infiltration of small round cells, an abscess forms. Only rarely does the abscess become large or rupture. Practically all cases show regression of the acute lesion followed by cicatrization. If sufficiently extensive no discharge of spermatozoa can occur, but sexual activity is undisturbed and atrophy of the testis does not necessarily follow.

Non-gonorrheal acute epididymitis and orchitis is usually due to staphylococcus aureus or colon bacillus, much more rarely to other organisms. It may

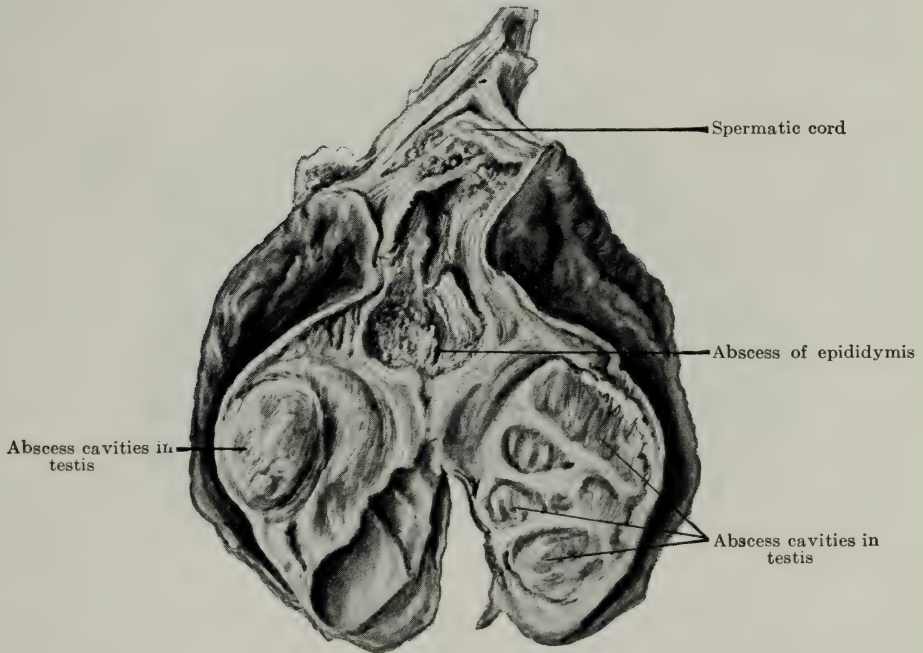


FIG. 347—Suppurative epididymo-orchitis (Laboratory of Surgical Pathology, Univ. of Penna.). From Genito-Urinary Surgery, by Martin, Thomas and Moorhead.

rarely follow non-gonorrheal urethritis, but is most commonly secondary to cystitis complicating enlarged prostate or urethral stricture. Often a seminal vesiculitis intervenes. The involvement of epididymis and testis has much the same situation and histologic features as the gonorrheal form. Onset may be rapid or may be so slow as to resemble that of tuberculosis. Spontaneous retrogression and cicatrization occur, but not infrequently the suppuration extends and is either incised or ruptures. Extension into the abdominal cavity is uncommon. Rare cases of fulminant epididymitis and orchitis are reported, and the process may also be gangrenous.

Metastatic acute infections are observed in the epididymis, more especially in septicemias and pyemias, in typhoid fever, cerebrospinal meningitis, etc. The same is true of orchitis, which also occurs in smallpox and typhus fever.

Of particular interest is the so-called metastatic orchitis of mumps, occurring usually in patients at the time of puberty. The lesion is apparently non-suppurative but in a considerable number of cases leads to fibrosis and atrophy of the testis. Orchitis usually appears at the end of the first week of the epidemic parotitis, but may rarely occur without parotid involvement (Keyes).

Chronic Inflammations.—Fibrosis of the testis may be visible in gross cross section or may only be inferred by difficulty in stripping out the tubules by a forceps. Microscopically, there is a form that can only be called fibrosis testis, in which there is partial or complete disappearance of epithelium with increase of interstitial connective tissue, often hyalinized where it surrounds the tubules. On the other hand, there may be a similar lesion with extensive infiltration of lymphoid and plasma cells, an indication of a progressive chronic orchitis.

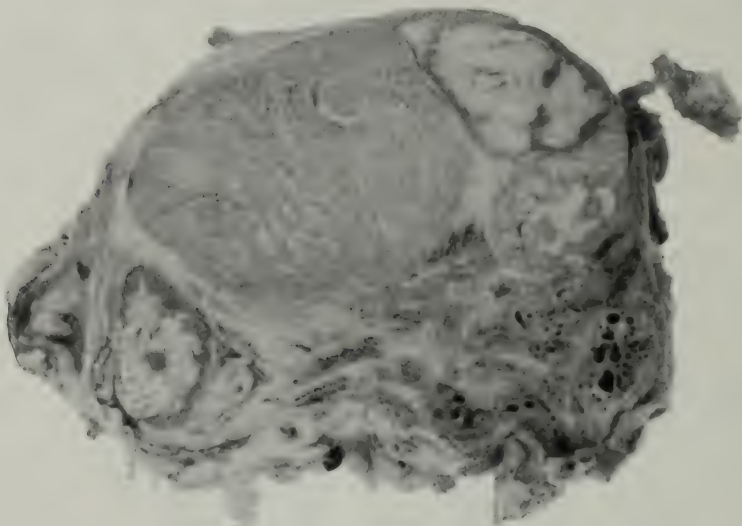


FIG. 348.—Tuberculosis of epididymis. Army Medical Museum 2622.

The lesions may be local or diffuse, unilateral or bilateral. The cause is not known except that certain cases are due to syphilis and others accompany passive hyperemia and wasting diseases. As a rule, the epididymis is not involved. Fibrosis there is usually the cicatrix of a preceding acute inflammation.

Infectious Granulomata. Tuberculosis.—The development of conglomerate tubercles is the more common mode of tuberculous affection of the epididymis and testis. The lesions may occur at any time of life. There is considerable difference of opinion as to whether or not tuberculosis may be primary in epididymis and testis. The common occurrence of tuberculosis of the lung makes it difficult to demonstrate a lesion in the testis without some minor lesion in the lung or in some other part of the body. It is difficult to understand how tubercle bacilli can gain access to the testis without involvement elsewhere, because it is generally admitted that primary infection through coitus is extremely rare if it ever occur. Many cases also show involvement elsewhere in the urogenital system, and it is often impossible to say whether

the involvement is primary in one place or the other. There is little doubt that a preceding attack of gonorrheal epididymitis predisposes to the lodgment of tubercle bacilli. Beginning in the epididymis as the first point of attack in the urogenital system, the disease may be disseminated to that system and thence generalized throughout the body. It is ordinarily first observed in the globus minor of the epididymis. It is stated that early in the lesion there may be simply a small yellow mass of necrotic material visible grossly, which microscopically shows desquamated epithelium, leucocytes, fat globules, and large numbers of tubercle bacilli. At any rate, a small tubercle with typical characters develops, and subsequently extends by the formation of daughter tubercles with fusion. This may retrogress and become calcified. More commonly it progresses and is likely to involve tunica vaginalis and testis. The resulting inflammation in the tunica vaginalis may provide either serous or serofibrinous exudate, and occasionally a purulent or caseous purulent exudate. This may extend further, involve and penetrate through the skin with the establishment of tuberculous fistula. Involvement of the testis is usually by direct extension and may ultimately destroy the entire organ. More especially in the later stages, the vas deferens and surrounding tissue are involved by the formation of a number of relatively small tubercles. The lesion primarily is unilateral and when the other testis becomes involved it is usually by way of a tuberculosis of the seminal vesicles and prostate. Although sexual activity is undisturbed, the patient is usually sterile even although only one testis is involved. The lesion is rarely observed first in the testis, except in case of generalized miliary tuberculosis of infants and children. Here the lesion is usually primary in the interstitial tissue. Sometimes, however, a diffuse tuberculous granulation tissue is produced which renders diagnosis extremely difficult. These lesions may also regress and undergo cicatrization, sometimes with small areas of calcification.

Syphilis.—In contrast to tuberculosis, syphilis is commonly first observed in the testis and involves the epididymis secondarily. Two forms of acquired syphilis are recognized, namely, the gummatous form and diffuse fibrous orchitis. As a rule, however, fibrosis accompanies the gummatous form. The gumma may be single or multiple, and variable in size. It shows the usual elastic consistence and the cut surface bulges. Histologically, there is the usual picture of gumma with complete necrosis of the testicular tissues surrounded by round cell infiltration. Not uncommonly the tunica vaginalis is involved, with the production of a moderate amount of serous exudate, and after cure of the lesion there may be extensive adhesions in the tunica vaginalis. The gummatous process may extend and involve the epididymis, but it is only rarely that it is primary in and confined to the epididymis. The diffuse lesion is likely to lead grossly to an increase in density in the organ and difficulty in stripping the tubules with a forceps. It may be diffuse or somewhat localized. According to Warthin, the earlier and more active diffuse lesions show an infiltration of plasma and lymphoid cells in the interstitial connective tissue, fibroblasts, diminution of spermatogenesis, thickening of

the basement membrane, and the presence of *treponema pallidum*. In the later lesions there is diffuse fibrosis of the interstitial tissue, with preservation and sometimes enlargement of the interstitial cells, fibrosis and hyaline transformation of the tissue immediately around the tubules, degeneration, necrosis and even disappearance of the epithelium with reduction in size of the tubules. In this stage it is extremely difficult to demonstrate *treponema pallidum*. In the late cases there may be loss of sexual power and of fertility, but the gummatous process may be fairly extensive without loss of either.

Leprosy.—Involvement of the testis in leprosy is not at all frequent, but when it occurs usually results in a diffuse fibrosis, subsequently with destruction of the epithelial cells of the tubules. Both within the tubules and in the interstitial tissues typical lepra cells, rich in bacilli are to be found. Simmonds describes the presence of lepra bacilli within the tubules and the interstitial tissues of the epididymis without, however, definite lesions in this structure.

Tumors.—In addition to the possible points of origin of tumors in other organs, the testis presents also the possibility of origin from totipotential sex cells, with more or less complicated arrangement of the descendant cells which constitute the tumor (see Dew). It is, therefore, possible that tumors which appear to be constituted of only one type of cell, really represent the preponderant growth of one element of a tumor which was primarily teratoid in character. Thus, an adenoma might represent the outcome by preponderance of a tumor originally containing cells derived from all three embryonal layers. It is admitted, however, that certain simple tumors may arise quite independently of other preceding tumors. These include the fibroma of the epididymis, the leiomyoma of the epididymis and perhaps also of the gubernaculum or cremaster, and in addition, presumably, the adenoma of the seminal tubules. It is also conceivable that sarcoma may be derived from these structures. Differences of opinion exist as to whether or not the interstitial cells may give origin to characteristic tumors; if so, the occurrence must be extremely rare. It is impossible to present any classification which is uniformly acceptable. The two schools of opinion, however, may well be represented by the classifications suggested by Schultz and Eisendrath and by Ewing. The former divide these tumors into homologous and heterologous groups. In the homologous group are included those benign tumors of epithelial and mesoblastic origin which have been mentioned. The malignant tumors include the epithelial group, using the term epithelial in its broadest possible sense, and covering the embryonal carcinoma which in many respects is similar to the spermatocytoma except as to origin, the trophoblastic chorionepithelioma, the hypoblastic adenomatous tumor and the epiplastic tumors including those of basal cell and of neurocytoma types. The mesoblastic type is represented by the teratoma which has undergone sarcomatous change. Ewing expresses the view that many of the tumors considered above as homologous tumors originate from differentiated cells, and that practically all the others originate from totipotential cells, but that one or another cell type may predominate in the developed tumor. Thus, all those tumors included by Schultz

and Eisendrath in the heterologous group, would represent tumors of teratomatous character in which differentiation has occurred to greater extent along one or two directions. For example, the chorionepithelioma would not be regarded as a pure tumor but rather as a mixed tumor in which this particular element predominates.

The greatest discussion centers about the nature and derivation of the large round cell tumor of the testis which is the most common tumor of this situation. This tumor is usually unilateral and although, appearing principally in early adult life, may occur at any time, grow either rapidly over a few months or a year, or slowly over several years, or show intermittent periods of growth. Such a tumor often arises first in the rete and then invades the rest of the organ. At first the form of the testis is preserved but later the mass becomes irregularly nodular. In cross section it is a soft, bulging, pallid tumor with various degrees of necrosis. Histologically, it is usually an alveolated tumor, although in some instances the alveoli are not well marked. The essential cells are large, polyhedral or spherical, with well defined cytoplasm and a moderately large vesicular nucleus. There are numerous mitotic figures. Vascularization is not rich and is contained principally within the fibrous tissue trabeculae. Ewing is of the opinion that all these tumors are derived from totipotent or perhaps only slightly differentiated cells, and that in the course of the growth of the tumor other elements are more or less obliterated. Schultz and Eisendrath, however, would separate two groups; in one the tumor is supposed to originate from the differentiated cells of the spermatoc tubules and is a genuine carcinoma, which they call spermatocytoma; in the other, the conception of Ewing is adopted, but it apparently is necessary to demonstrate remnants or parts of other types of tumor growth in order to identify this as the embryonal carcinoma. From a somewhat limited material we agree with Ewing that these large cell tumors of the testis should all be regarded as embryonal carcinoma.

The teratoma of the testis is a mixed tumor containing a wide variety of elements traceable to the various embryonal layers. Ordinarily this tumor progresses slowly and becomes serious when one or more of its elements become malignant. The dermoid cyst of the testis is like that in any other situation.

Metastasis of malignant testicular tumors may sometimes be by the blood stream with distant foci of secondary growth, but is more commonly by way of the lymphatics to the lymph nodes of the retroperitoneal region, either low in the abdomen or about the celiac axis. Sometimes the secondary growth in this situation is extremely large without further metastasis, but it is also possible for metastases to be widely distributed. In our experience the metastases of the malignant teratoma usually represent one type of cell proliferation, but it is also true that the secondary growth may be extremely complicated in structure. The chorionepithelioma may occur as a small growth in the testis, sometimes not observed clinically, but with extensive, large and complex metastases throughout the body.

SEMINAL VESICLES

The general retrogressive changes include especially atrophy and fibrosis in old age and following chronic inflammations. Severe arteriosclerosis may lead to hemorrhages into the vesicles. Acute seminal vesiculitis may be an extension from neighboring structures, as urethra, bladder and prostate, or may be hematogenous as in septicemia and pyemia. The extension forms begin as a catarrhal inflammation and may become purulent. Cicatrization following the vesiculitis and the commonly associated perivesiculitis, may result in marked atrophy or complete disappearance of the vesicle. Cicatricial obstruction may result in cyst formation. According to Simmonds, tuberculosis occurs more often in the seminal vesicle than in any other part of the genital tract. It may be unilateral or bilateral. It begins as miliary tubercles of the wall, which fuse, involve the mucous membrane and produce a caseous purulent inflammation. Tubercles are usually found in the neighboring peritoneum. Extensions to prostate and bladder are common. Tuberculous abscess of the perirectal tissues may be followed by perineal fistula.

The commonest tumor involvement is by extension from malignant tumors of prostate, bladder and rectum. Fibroma, primary carcinoma and sarcoma are reported (see Hinman and Gibson).

THE PROSTATE

Retrogressive Changes.—Degenerations of the epithelium occur in connection with those of systemic diseases causing such changes elsewhere. There may be amyloid in the vessel walls, hemosiderin deposits, or extensive pigmentation in hemochromatosis. Corpora amylacea have been discussed in the chapter on degenerations and infiltration. These concentrically laminated, sometimes radially striated, acidophilic bodies are common in the acini of the glands after adult life has been reached, and may increase in number and size in various pathological conditions. Sometimes small calcareous concretions are observed in the acini and these rarely may lead to secondary inflammatory changes. The organ is likely to undergo atrophy in old age, but rarely does chronic inflammation lead to any notable atrophy.

Inflammations.—Acute prostatitis is ascribed to a very large number of causes, but especially important are those borne by the blood stream as in septicemias and pyemias, and by extension from neighboring organs. The latter group of causes seem by far the most important. When the infection is hematogenous there are usually multiple small abscesses, although sometimes they may attain considerable size. The staphylococcus aureus is the most common organism identified. There is usually an associated seminal vesiculitis and often an acute epididymitis. Acute prostatitis most commonly arises as the result of extension from neighboring foci of inflammation. By far the commonest cause is gonorrhea. Inflammations of the bladder may involve the prostate by extension along the mucous surfaces. Trauma and infection of the urethra by catheterization are common causes. Although cocci

of various kinds may be found, the bacillus coli communis is the most common organism. Wilson and McGrath differentiate a catarrhal, a follicular and a parenchymatous (or preferably diffuse) form of acute prostatitis. Acute catarrhal prostatitis is a common accompaniment of gonorrhea and produces catarrhal inflammation of the prostatic acini and ducts. This may clear up, may at times become chronic, or because of obstruction to outlets there may be an accumulation of desquamated cells and exudate within acini, finally leading to suppuration. It is then called a follicular prostatitis because the suppuration is confined within the acini, but there may be extension into the supporting tissue in the prostate with true abscess formation. Less frequent than these is acute diffuse prostatitis in which there is extensive hyperemia, edema and moderate cellular infiltration of the entire prostatic substance.

Chronic prostatitis is most often confined to the region of the caput gallinaginis where there is a chronic catarrhal inflammation, sometimes associated with small papillary outgrowths of epithelium.

Tuberculosis.—Although leprosy and syphilis may exhibit prostatic involvement the nature of the lesions is not well known. Tuberculosis is the most frequent and most important of the infectious granulomata in the prostate. The organ may be involved through the blood stream or the lesion may be secondary to tuberculosis elsewhere in the urogenital tract. According to Simmonds the prostate is attacked more frequently than any other part of the urogenital tract except the seminal vesicle. The organisms may be carried from epididymis and testis by the secretions, and the process may extend from the seminal vesicles either by the ducts or through the lymphatics. Usually one side of the prostate is involved more than the other but this is not always the case. The tuberculosis begins in the glandular substance with the formation of miliary tubercles which enlarge, extend and produce irregular, usually multiple, caseous masses. Secondary infection, especially by the bacillus coli communis, is not uncommon, and there may occur a secondarily infected tuberculous abscess, which can rupture into the bladder or urethra or extend more widely through the pelvic tissues.

Enlarged Prostate.—This is the most common lesion of the adult prostate gland. The nature of the condition is not clearly understood and various names are employed. Hypertrophy of the prostate is the most commonly used term but there is much doubt that this is correct. The lesion is more in the nature of a diffuse hyperplasia. The enlargement is usually moderate but may exceed a weight of 200 grams. There are, however, forms in which the organ showing all the characteristic microscopic changes, may be somewhat reduced in size. Sometimes the organ is a large, smooth, dense, but elastic body. More often, however, it is nodular and may be diffuse or involve either the lateral lobes, the middle lobe or the anterior lobe, which last represents the glandular tissue about the verumontanum. As a rule, the enlargements involving the middle lobe are due almost entirely to hyperplasia of the glandular acini. In cut section the character depends upon the important elements contributing to the enlargement. Thus, if the stroma be the important part the

cut surface is glossy, firm, somewhat elastic and pallid, whereas if the glandular elements be involved the cut section may be spongy and of adenomatous character. Microscopically, there are variable degrees of hyperplasia of glands, hyperplasia of connective tissue and increase in the amount of muscular tissue which also is probably to be regarded as a hyperplasia. It is only with extreme rarity that the muscle elements proliferate so as to constitute a true leiomyoma. The glandular hyperplasia not infrequently simulates very closely a nodular variety of adenoma, but in our experience is more often a diffuse adenomatous hyperplasia. The acini are increased in number, irregular in outline and sometimes distinctly dilated. The epithelium may be in the

form of a single layer of cells, multiple layers of cells, and not infrequently shows papillary growth into the lumina. These acini may contain granular material or desquamated cells and a considerable number of corpora amylacea. The supporting tissue may be more or less distinctly infiltrated with lymphoid cells, a feature which is regarded by some investigators as indicating an inflammatory character of the lesion. Of the 387 cases studied by Wilson and McGrath, 300 showed an increase of both epithelium and stroma and 266 a round cell infiltration. Seventy showed an increase of the stroma alone, and seventeen an increase of the epithelial elements alone. Although enlarged prostate may rarely be encountered in early life it is practically always confined to patients of more than fifty years of age. In Wilson and McGrath's series



FIG. 349.—Enlargement of prostate, especially medial lobe, dilatation and hypertrophy of bladder, hydro-ureter and hydro-nephrosis. Army Medical Museum 30614.

all were over fifty years of age and 83 per cent. were more than sixty years of age. It has not been possible to show that victims of prostatism have a greater incidence of gonorrhea in the past than others. More than 90 per cent. of prostaties are, or have been married, but this probably applies equally to all the male population of this time of life. There is nothing which clearly indicates that either sexual incontinence or abstinence has any particular influence. Judging from the findings upon microscopic examination it would appear that the lesion is principally a hyperplasia, and in some cases this is presumably upon an inflammatory basis. Various hypotheses as to origin are outlined by Keyes. The supposition that arteriosclerosis is of importance as a cause is contradicted by the fact that more victims of arteriosclerosis escape prostatism than are afflicted. The supposition that the lesion represents a condition in the prostate similar to that of fibromyoma of the uterus is not

supported either by embryonal analogy or by the nature of the prostatic lesion, which is rather adenofibromatous than fibromyomatous. The supposition that failure of balance between inherent activity of testis and prostate is a cause is not supported by study of castrated animals or men. Hyperemia and inflammation are supposed to be causes, and it is at least possible as judged by the presence of lymphoid cell infiltration in many of these organs that inflammation may play a part. But the absence of this feature in many other enlarged prostates would indicate that inflammation is by no means a universal cause. Tumor-like characters sometimes appear in the glandular hyperplasia, but are extremely rare in the muscular overgrowth and practically never present in the fibrous tissue hyperplasia. The important sequels of prostatic enlargement include obstruction to outflow of urine from the bladder, and also the possibility of the glandular hyperplasia undergoing malignant change. Obstruction to urinary outflow leads ultimately to hypertrophy of the bladder. In numerous cases a small sac may form behind the enlarged prostate and may contain the so-called residual urine, namely that which cannot be expelled during urination. Infection of the bladder is likely to occur especially because of catheterization, and may be followed by extension of the infection along the ureter into the renal pelvis and into the kidney. Prostatitis also suffer from diminution of renal function. Although this may be due to damming back of urine through the ureters into the renal pelvis, as has already been discussed, it is also possible that it is due to reflex inhibition of urinary secretion, because the autonomic nerve supply through the sympathetic system is common to both the kidney and the base of the bladder (Bush).

Tumors.—Benign tumors of the prostate are distinctly rare. The adenoma is sometimes reported as an independent growth but is observed almost solely as a part of hyperplasia of the organ. Prostatic tumors occur mainly in adult and later life but may rarely occur in childhood (Sysak).

Carcinoma of the prostate occurs mainly as a sequel of enlargement of the prostate, but may occur independently. It is a disease of old men and may be revealed only by the microscopic examination of the enlarged prostate. By this criterion, carcinoma is said to occur in from 10 to 19 per cent. of the cases of enlarged prostate. The apparent recent increase in the incidence of cancer of the prostate is therefore due mainly to increased accuracy of diagnosis. When the carcinomatous process is well established, it usually progresses rapidly. An enlarged prostate may remain quiescent for a long period of time without showing evidence of carcinomatous change. When the process extends beyond the substance of the gland itself, it involves neighboring structures and the organ becomes adherent. It is usually a somewhat soft, nodular mass. Histologically, it differs from the adenoma in that the gland acini are more numerous, more irregular, more constantly filled with multiple layers of epithelium, and show invasion of the surrounding tissue in the form of solid cords. The epithelium becomes less typical as the process extends. Although it is possible to distinguish adenocarcinoma and carcinoma simplex, the former practically always has some of the elements of the latter type.

Sometimes, however, a pure carcinoma simplex is observed. In this case there are solid nests and bands of epithelial cells, usually in rounded form and extending widely through the supporting tissue. Uncommonly, scirrhous carcinoma may be observed, and in such cases the prostate is likely to be hard and small. Rare cases of squamous epithelioma of the prostate are attributed to remnants of the embryonal and fetal stratified squamous epithelium of the glands or to metaplasia of adult epithelium. The extension of prostatic cancer by way of the lymphatics is usually first to the seminal vesicles and then to the lymph nodes of the pelvis. Invasion of the bladder is not common because of the fact that the prostatic lymphatics do not drain into bladder lymphatics; the latter are not particularly numerous and there is little intercommunication. Only after extensive pelvic growth are the inguinal lymph nodes involved. In the more advanced cases the entire pelvis may be filled with a carcinomatous mass. A most significant feature of the metastasis of cancer of the prostate is that to the bones. Metastasis of prostatic cancers to bone is distinctly more frequent than that of other forms of cancer, including those of thyroid and breast. Furthermore, the prostatic metastasis shows a distinct tendency to induce osteoplastic reaction on the part of the bone.

Sarcoma of the prostate is distinctly unusual. Herrick's analysis of the cases reported shows that one third of the cases occur before ten years of age, three-fourths occur before forty years and that four-fifths occur before the age when prostatic cancer is likely to be observed. The round cell sarcoma is usually a lymphosarcoma. Ewing has found, however, that at least one such case was really a carcinoma, and this observation throws some doubt upon the other reported cases. Nevertheless, the fact that lymphomata of lymphatic leucemia may be found in the prostate makes it seem possible that lymphosarcoma may also occur there. Spindle cell sarcoma also occurs in the prostate but should not be confused with the tumors of spindle forms of epithelium. These tumors may be in the form of a pure spindle cell sarcoma or they may be myxomatous or angiomatous. Sarcoma of more differentiated cells also occurs and among them rhabdomyosarcoma of the prostate is reported. The sarcoma usually is a large, rapidly growing tumor, which invades widely in the region and may produce distant metastases.

Secondary tumors in the prostate arise usually by direct or lymphatic extension from malignant tumors of the bladder and rectum. It is only rarely that metastasis from more remote situations is observed.

FEMALE GENITALIA

Congenital Anomalies.—There are numerous malformations of the uterus, which depend upon anomalous development and fusion of the Müllerian ducts. Perhaps the simplest classification is that of Nagel (see Frankl) into four groups. Anomalies arising in earliest embryonal life are rare and include absence of uterus and vagina and completely separated double uterus. Graves states, however, that complete absence of uterus does not occur even though the vagina be absent. Anomalies of the second group arise after the formation

of the Müllerian ducts and include uterus duplex bicornis cum vagina septa, partial duplication with normal vagina but with a septum at the fundus (uterus subseptus uniforis), or a septum in the cervix (uterus subseptus biforis). This group includes also aplasia of one half of the uterus with production of uterus unicornis, and aplasia of the entire uterus with atresia of the vagina. The third group arises during fusion of the Müllerian ducts and includes uterus bicornis unicollis, uterus arcuatus (with lateral prolongations of the fundus and cavity toward the tubes) and uterus subseptus unicollis. The fourth group includes those anomalies which arise after formation of the uterus, such as the fetal and infantile types of uterus and imperforate cervix. Pregnancy may be impossible or complicated in the anomalous uterus. It is said that tumors of uterus and adnexa are more frequent in anomalous than in normal uteri.

The ovaries may fail to descend to normal position. Absence of ovaries occurs only in non-viable fetuses. Apparent absence may be due to detachment or misplacement in fetal life. Most cases of what appear to be accessory ovary are due to separation of a small part of ovarian tissue by torsion at a late period of fetal life, or inflammations or tumor pressure in postfetal life. True accessory ovary occurs rarely and, to be identified, must have an accessory tube. Hypoplasia of the ovary may be found in infantilism, and sterility is often the result. Grossly, it is usually small but may be large and is identified microscopically by the incomplete development of the follicles. The most important anomaly of the tubes is a torsion of the distal portions, which may cause sterility.

Anomalies of the vagina include developmental defects and those probably due to inflammations in late fetal life. To the former probably belong all cases of absence of the vagina, septation and complete doubling of the tube. Extensive atresia may be due to a failure of hollowing of the primary vaginal cord. Imperforate hymen may also be developmental. Other local atresias, or even complete atresia, as well as transverse membranes, are probably due to fetal inflammations.

The vulva may be absent but only in the non-viable fetus. Vulvar hypoplasia is seen in infantilism. Hypoplasia of various parts of the vulva may be encountered. Complete duplication of uterus and vagina may be accompanied by double vulva. In hypospadias the urethra opens into the vagina. Epispadias is rare; the urethra may open above the clitoris; increasing degrees of epispadias become finally exstrophy of the bladder. Hermaphroditism has been discussed with male genitalia.

THE VULVA

Circulatory Disturbances.—The labia participate in the edema of heart and kidney disease. Local causes of edema include inflammations, pregnancy and pelvic tumors. Dilatation of the veins, or vulvar varices, may occur in general passive hyperemias but is most common in pregnancy. The straining of labor may rupture the veins with the production of vulvar hematoma. Exclusive of labor, such hematoma is only rarely due to direct trauma.

The lesions of skin and muscle during labor are fully discussed in the texts on obstetrics.

Elephantiasis affects the labia majora and sometimes the labia minora with chronic swelling, increased firmness, irregularity of cutaneous surface. Ulceration and lymphorrhea may occur. Prolonged interruption of drainage as by chronic inflammations, extensive removal of inguinal lymph nodes or filariasis explain most cases. Others are unexplained.

Inflammations.—Acute vulvitis of adults may be either catarrhal, mucopurulent or ulcerative. It is not common because of the resistance of the surface epithelium to injury. It may be caused by the irritation of scratching, masturbation, excessive or violent coitus, and more especially by the irritation of discharges from vagina and uterus, and by the irritation of urine, especially that in diabetes. The vulva may be involved in such infectious diseases as smallpox, scarlatina, diphtheria, dysentery and typhoid fever. Gonorrhea is rarely a cause of vulvitis in adults. In children both gonorrheal and non-gonorrheal vulvitis are common. Inflammation of the glands of Bartholin is a frequent complication. The parts are red, swollen and covered with mucus or exudate. Tenderness, pain and pruritis may be present. Edema may be prominent in the labia minora. Ulceration is more common in postpartum streptococcus infections and may be followed by gangrene. Gangrene may also be due to serious infectious diseases or to trauma, and may be a manifestation of noma.

Chancroidal ulcers are usually multiple and appear especially about the frenulum. They are similar to those described as occurring on the penis and also are frequently complicated by inguinal lymphadenitis.

The catarrhal and gonorrheal inflammations may become chronic. Perhaps also to be classified as chronic inflammatory lesions are two conditions peculiar to the vulva, kraurosis and esthiomene.

Kraurosis vulvæ occurs at any time in adult life and has no known cause, although it may be preceded by prolonged irritation from discharges or by pruritis. There is shrinkage and stiffening of the parts with marked flattening, dryness and pallor of the skin. The hairs often disappear. The lesion is usually clearly defined from the surrounding skin. Histologically, the epiderm is thin, the papillæ flattened, the corium densely fibrosed and infiltrated with lymphoid and plasma cells; especially characteristic is the fact that the elastic tissue completely disappears. Hair follicles, sebaceous and sweat glands undergo atrophy and may disappear. Kraurosis is frequently followed by cancer. It may be confused with Paget's disease or may possibly be one phase of that lesion. In Paget's disease, however, atrophy is not so marked, low grade inflammation is more prominent and the intermediate zone of the epiderm shows the characteristic large cells.

Esthiomene is a chronic eroding ulceration of the vulva. It is usually anterior or posterior to the vagina but may appear in any part of the vulva. It is accompanied by marked chronic swelling, especially of the labia minora, upon which the ulcers may be symmetrical. Its nature is obscure. Histo-

logically it is said to show, under a defect of the surface epithelium, rich infiltration of lymphoid and plasma cells and the formation of multinucleated cells. Stein regards the lesion as a syphiloma or more exactly a gumma, usually appearing late in the disease and independently of other syphilitic manifestations. The lesion is sometimes called rodent ulcer but is not a tumor.

Infectious Granulomata.—Tuberculosis is uncommon. It may occur as a lupus, rarely as miliary tubercles, or as a conglomerate tuberculosis with a disposition to marked and irregular enlargement of the labia with ulceration.

Syphilis.—Chancre is rare on the vulva, but when it occurs is usually found on the labia majora. Mucous patches on vulva and neighboring skin are common and may occasionally be converted into deep ulcers. Gumma may rarely attack any part of the vulva. The probability that esthiomene is a gumma has been mentioned.

Tumors.—Fibroma, fibromyoma and lipoma may occur in various parts of the vulva. The lymphangioma and hemangioma should not be confused with varices of the labia majora. Pigmented nevi are common upon the labia majora and may become malignant melanomas. For convenience the acuminate condyloma is mentioned here. As in the male, it is due principally to irritant discharges. It occurs often in multiple form and may be found at the vaginal orifice or about the labia minora. Of interest is the fact that the labia majora may show fibroma, fibromyoma and adenofibroma of the pre-inguinal part of the round ligament. The sweat glands and the glands of Bartholin rarely give origin to adenomas.

Squamous epithelioma of the vulva originates in the clitoris, at the orifice of urethra or in the sulcus between the labia. Grossly, it may be a flat, ulcerative, firm mass, a rapidly progressing ulcer, or a cauliflower-like growth. In contrast to carcinoma of the penis, metastasis to the inguinal and iliac lymph nodes occurs early in the disease (see Taussig). The rare adenocarcinoma probably originates in the glands of Bartholin. Malignant melanoma of the vulva usually produces early and widespread metastasis.

Sarcoma is rare, usually diagnosed only upon microscopic examination and may be of round cell, spindle cell or more highly differentiated types.

Teratoid tumors including the dermoid cysts are rare.

Cysts include those of Bartholin's glands (Cullen), cysts of the hymen, cysts of sebaceous and other glands. Echinococcus cyst has been reported.

THE VAGINA

Circulatory Disturbances.—Local and general passive hyperemia may produce varices in the vaginal wall. Hemorrhage may be due to ruptured varices, to trauma by instruments and foreign bodies introduced for various purposes, to labor, to violent coitus. Large clots may form in the vagina and be discharged. Hemorrhage into the vaginal tissues (hematoma vaginæ) may infiltrate widely in the pelvic and retroperitoneal tissues. Accumulation of menstrual or other blood in the vagina behind zones of atresia is called hematocolpos.

Inflammations.—The commoner forms of vaginitis or colpitis run a somewhat prolonged course and are subacute rather than acute. The mucous membrane is hyperemic and swollen, especially at the crests of the folds. The exudate is mucous, mucopurulent or purulent, but may be fibrinous or hemorrhagic. Ulceration is not uncommon. Gonorrhea is a common cause in children but not in adults. In the latter when present it affects the upper part of the vagina in continuity with the cervix. Aschoff refers to the presence, especially in the vaginitis of childhood, of large granular cells resembling trachoma bodies. The granules are probably degenerated gonococci but may be of some other nature not necessarily gonorrheal. Other organisms which may cause vaginitis include staphylococci, streptococci, colon bacilli, etc. present in, or introduced into, the vagina but exhibiting virulence only when the vaginal surface is abraded or wounded. Various fungi may produce low grade vaginitis. Animal parasites may irritate, especially the oxyuris vermicularis. Graves speaks of an ameba urogenitalis as pathogenic. *Trichomonas vaginalis* is rarely irritative. *Distomum hematobium* may invade from the bladder. Numerous non-pathogenic spirochetes are described (Noguchi and Kaliski). The presence of foreign bodies, such as neglected pessaries, may produce vaginitis, sometimes ulcerative in character. Most important are irritative or corrosive douches. Discharges from endocervicitis or from putrefying tumors of the cervix or fundus of the uterus, may be extremely irritant.

Various forms of vaginitis are described. In addition to the catarrhal and suppurative forms, there is a nodular vaginitis in which small projecting nodules are made up of focal accumulations of lymphoid and plasma cells, a papillomatous vaginitis in which minute papillary projections of epithelium are thrown up, and a macular form in which there are numerous small areas of hemorrhage or blood pigment in healed or still existent minute erosions. Pseudomembranous vaginitis may be a true diphtheria, may be an accompaniment of other infections such as variola, cholera, dysentery, etc., or may be a part of puerperal infection. Emphysematous vaginitis is a condition, usually postpartum, in which small gas-containing vesicles occur in the vaginal wall, of little significance and probably due to slight invasion of gas-forming bacteria. Exfoliative vaginitis is rare; casts of vaginal mucosa are separated and discharged. It is usually due to corrosive chemicals but may be a part of membranous dysmenorrhea. The more severe inflammations may lead to involvement of the surrounding parts, a paravaginitis, usually suppurative or phlegmonous. Extensive gangrenous vaginitis may occur, and rarely noma involves the vagina.

Infectious Granulomata.—Tuberculosis of the vagina, without neighboring involvement, is rare and occurs practically only as hematogenous miliary tuberculosis. Infection by coitus is doubtful. Ulcerative lesions may extend from the vulva as in lupus or from the uterus or other organs in extensive urogenital tuberculosis. Primary lesions of syphilis are rarely seen and secondary mucous patches are probably often overlooked. Gumma is more likely to extend from neighboring structures than to originate in the vagina.

The cicatrization of syphilitic lesions may result in marked deformity of the vagina.

Tumors.—The benign tumors are rare and include the fibromyoma and myoma. The papillæ of papillomatous vaginitis may become tumor-like in character. The acuminated condyloma also occurs in the vagina. An important tumor is the adenomyoma of the rectovaginal tissues. This may attain considerable size and is difficult to remove. It is supposed to originate from uterine mucosa or remnants of the Müllerian duct, but it is possible that some are the endometrial implants described by Sampson, to be discussed with diseases of the ovary.

Carcinoma of the vagina is usually a squamous epithelioma, and although an uncommon lesion is seen most often in the upper posterior wall. It is an eroding ulcerative mass with metastasis to the regional nodes. Adenocarcinoma is extremely rare and is supposed to arise from embryonal remnants. Carcinoma of the cervix often extends to the vault of the vagina.

The sarcoma of the adult vagina may be of any variety. Of particular interest is a congenital type of mixed or teratoid tumor, the grape-like sarcoma or sarcoma botryoides. It occurs most often in childhood but may occur in adult life. It may originate in the cervix uteri or in the vaginal vault. It may infiltrate widely but grows principally in the vagina as a mass of firm, pink, glossy, small ovoid or grape-like bodies. Necrosis may result in extensive sloughing and putrefaction. Histologically, the tumor is a mixture of connective tissue, often myxomatous, smooth muscle and the embryonal type of striated muscle. It may or may not be richly vascularized and even though highly invasive may not show the histological characteristics of sarcoma.

Metastatic tumors, other than the direct extensions of neighboring malignant tumors, are rare. Of interest is the chorionepithelioma which often leads to metastatic growths in the vagina, nodular, dark red, rapidly growing, bleeding tumor masses, with the typical microscopic character. The original uterine tumor may be small and difficult or impossible to find.

Cysts.—Cysts of the vaginal wall are fairly common. They may vary in size from a diameter of a few millimeters to several centimeters, are lined by low cuboidal or flattened epithelium, and are filled with a clear or cloudy mucinous fluid containing desquamated cells and often cholesterol. They may originate from glandular embryonal inclusions in the vaginal wall, from remnants of Gärtner's duct, or in case of double anomalies of vagina and uterus, may be cystic dilatations of a remaining Müllerian duct or rudimentary vagina.

Fistulæ may exist between vagina and urethra, bladder or rectum. Thus, urine or feces may be discharged through the vagina. Fistulæ are most often caused by tissue necrosis due to birth injuries, although their incidence is being reduced by improved obstetrical practice. They may result from infections in operations, from abscesses of various kinds and from the invasion and necrosis of malignant tumors.

Alterations of Size and Position.—The most important dilatations are those due to retention of fluids behind an atresia. Pyocolpos is usually due to

accumulation of pus in inflammations. The congenital atresias and alterations of form have been noted. Acquired atresias are usually the result of acute inflammations, wounds, or syphilis.

The most important alterations of position are those due to failure of support. The pelvic viscera are maintained in position principally by the integrity of the muscles and fascias of the pelvic floor. Failure of support is usually due to lacerations of the muscles and fascias from injuries in labor, although wounds, other injuries and tumors may produce the same effect. As a rule, the loss of support affects first the anterior vaginal wall, which sags backward and downward and may project through the vaginal orifice, producing partial prolapse of the anterior vaginal wall. With it goes the floor of the bladder, producing cystocele. In the more severe lacerations the posterior wall may also be involved and sags downward and forward, as a partial prolapse of the posterior vaginal wall. Bulging of the rectum is rectocele. Protrusion of the vaginal wall through the introitus constitutes prolapse of the vagina. Uncomplicated vaginal prolapse is uncommon, for as a rule when this degree of failure of support is reached, the uterus has become more vertical by retroversion, the isthmus elongated, the whole uterus displaced downward in a partial prolapse of the uterus, which is associated with the vaginal prolapse. The cervix or indeed the entire uterus may project through the vaginal orifice to constitute procidentia, usually associated with eversion of the vagina and partial or complete inversion of the uterus. The surface epithelium of the vagina becomes keratinized and the lining membrane of the uterus transformed to squamous epithelium. Genital prolapse may permit of hernial projection of intestinal loops to constitute enterocele or hernia vaginalis. Much the same condition may be produced by congenital anomaly of the pouch of Douglas, permitting the intestinal loops to descend as far as the perineal floor.

THE UTERUS

Circulatory Disturbances.—Passive hyperemia of the uterus may be due to general causes such as chronic heart disease, to local causes which produce pressure upon the pelvic veins as, for example, the presence of tumors in the pelvis, or damming back of blood in the uterus itself because of alterations in form or position. Thus, a vertical or posterovertical position of the uterus, retroversion, a bending of the uterus upon itself, a retro- or antelexion, or a descent to a low position in the pelvic cavity, prolapse, may prevent the free outflow of blood from the organ and produce passive hyperemia. Secondary to all these conditions there may be edema of the uterus which is most evident in the endometrium. Edema of the cervix may be due to passive hyperemia, to inflammation in that region, or may be the result of pregnancy.

Hemorrhage from the uterus is normal in the menstrual period. The various disturbances of the physiological function of menstruation are discussed adequately in the textbooks on obstetrics. Severe or prolonged menstruation is referred to as menorrhagia. In contrast to this is metrorrhagia or hemorrhage not incident to menstruation. This is a common clinical mani-

festation and may be due to a wide variety of causes. It sometimes occurs in the passive hyperemia of heart disease. Hyperpalsia of the endometrium may produce either menorrhagia or metrorrhagia. Metrorrhagia may also be due to traumatism, to local inflammations, to poisons such as phosphorus, to malignant tumors, or may be a local manifestation of general acute infectious diseases. Benign tumors, either growing in the wall of the uterus or growing into the cavity as polyps, may produce only menorrhagia, but occasionally they produce metrorrhagia. Metrorrhagia of older women, after they have passed the menopause, has as its most important cause malignant tumors of the uterus. Nevertheless, cases occur in which the lesions commonly productive of hemorrhage are not present, and examination of the uterus shows only the atrophy of age and pronounced arteriosclerosis with extensive medial disease. Usually the hemorrhage is attributed in some indirect way to the presence of the arteriosclerosis, but since many uteri exhibit arteriosclerosis without having an associated metrorrhagia, it is somewhat doubtful that arteriosclerosis is a cause. Hemorrhage during pregnancy is usually due to the detachment of the placenta, as a rule, because of the development of the placenta near the cervix instead of in the fundus.

Inflammations.—Inflammations of the uterus may involve the endometrium, endometritis, the wall of the uterus, myometritis, the peritoneum covering the uterus, perimetritis, and the broad ligaments, parametritis. These are all more or less interrelated and begin as a rule in the endometrium. Endometritis may affect the lining of the fundus in a somewhat different way from that of the cervix; in other words, true endometritis may differ somewhat from endocervicitis. There is also a great difference in susceptibility to inflammation on the part of the non-pregnant uterus and the pregnant uterus. With the exception of gonorrhea, inflammations of the non-pregnant uterus are unusual. In acute gonorrhea the lining of the cervix is more markedly affected than is that of the fundus. Gonorrheal endocervicitis is in the earliest stage an acute catarrhal inflammation with a large amount of mucous secretion in addition to the exudate. Subsequently, it becomes more distinctly purulent and quantities of greenish-yellow pus are discharged. In this stage the mucosa resembles very much that of the male urethra as regards the pathological changes. There is rich infiltration of leucocytes throughout the endometrium and the glands are likely to show an excess of mucus. As the disease decreases in severity, a chronic catarrh of the cervical mucosa with the discharge of a thick, glairy mucus containing relatively few pus cells or gonococci is likely to develop. Although the endometrium of the body of the uterus may harbor gonococci for long periods of time, it is unusual for acute inflammations to develop in the non-pregnant uterus. The organisms live and grow and pass on into the Fallopian tubes with little or no involvement of the fundal endometrium. Nevertheless, the changes incident to pregnancy or to puerperium may serve to excite a severe gonorrheal endometritis which may go on to involvement of the muscle, a true gonococcal myometritis (see Gurd). In this condition there are large numbers of gonococci and a rich infiltra-

tion of leucocytes, mucoid degeneration, desquamation and necrosis of the glands.

Acute, subacute and chronic catarrhal endocervicitis is not uncommonly due to causes other than gonorrhea. Rich mucous secretion constitutes the condition spoken of as leucorrhea. It may be found at almost any period of life, and is often without definite cause other than malposition of the uterus or exposure to cold. It is not confined to parous women and may even occur in virgins. In the subacute and chronic forms the cervix, in addition to the rich secretion of mucus, may show retention cysts of the mucous glands, the so-



FIG. 350—Acute suppurative endometritis and metritis, in the puerperium. *Staphylococcus aureus* septicemia. Army Medical Museum 30792.

called Nabothian cysts. Such cysts, however, may be seen in women who do not have cervical catarrh.

Acute *edometritis*, not of gonococcal origin, is unusual in the non-pregnant uterus. It may be caused by retained products of pregnancy such as fragments of placenta, necrosis of polyps and endometrial tumors, retention of menstrual blood and irritation by instrumentation and various therapeutic washes. It is generally thought that when inflammation occurs under these circumstances it is due to infectious organisms ascending from the vagina. The inflammation may be catarrhal or purulent. It may progress so as to involve the wall of the uterus and the surrounding structures, although such an extension is rare. Occasionally, due to the more violent methods of treatment such as cauterization of the cavity of the uterus, infection of tumors, more especially carcinoma, and accompanying acute infectious diseases such as diphtheria,

typhoid fever and cholera, acute fibrinous or fibrinopurulent endometritis with extensive necrosis of the endometrium occurs. This, of course, is more likely to be followed by invasion of the wall of the uterus and the surrounding structures than are the simpler forms. The condition must not be confused with *membranous dysmenorrhea*. This condition occurs more especially at the menstrual period and in infantile forms of uterus, and is characterized by the discharge of the lining of the uterus in the form of a cast. Microscopic examination of the material shows that it is made up in most cases of the compact and spongy layers of the endometrium, the basal layer remaining in the uterus. Occasionally all three layers are discharged. The interstitial cells of the tunica propria are often swollen and resemble very closely those of decidua. If necrosis has preceded the desquamation of the membrane, there may be a considerable infiltration of leucocytes, but many cases are observed without any leucocyte infiltration whatever.

The puerperal uterus, whether following full time pregnancy, miscarriage or abortion, is especially susceptible to infection because of the open cervix and the raw surface left by the placental detachment. The organisms most frequently encountered are the streptococcus, staphylococcus, and sometimes the gonococcus latent in the endometrium. Occasionally, low grade infection of the puerperal uterus occurs because of saprophytic invasion of retained placenta. This really constitutes a gangrene of the retained placenta and the victim may suffer from absorption of the products of decomposition, the so-called sapremia. Independently of this, or following it, there may occur a serious infection. The pyogenic organisms gain access readily to the dilated veins of the endometrium and myometrium and set up the most profound and serious inflammation. There may be a violent purulent endometritis, or a fibrinopurulent endometritis, either of which may be accompanied by extensive necrosis of endometrium and underlying layers of myometrium. This process may extend by continuity into the Fallopian tubes and thence to the peritoneum, or by contiguity into the walls of the uterus, and thence into the parametrial tissues and peritoneum. Usually, the condition develops into a septicemia or even pyemia.

The healing of acute endometritis may lead to extensive cicatrization of the endometrium, sometimes with adhesions. It is also probable that the inflammation may result in the so-called chronic atrophic endometritis, in which there is thinning of the endometrium with atrophy of the glands and overgrowth of interstitial tissue of the tunica propria. The inflammatory nature of such an atrophic state is indicated by infiltration of plasma cells and lymphoid cells and the presence of blood pigment. This must not be confused, however, with the simple non-inflammatory atrophy and fibrous overgrowth of the senile uterus.

Much more frequent among the chronic lesions of the endometrium is that spoken of as *endometrial hyperplasia*, a condition formerly called chronic hyperplastic endometritis. There are probably some cases which represent the chronic course of inflammations such as those produced by gonococcus,

but in many instances the cause is obscure. Passive hyperemia of the uterus such as may be caused by malposition or by extensive pelvic adhesions, is perhaps the most common cause, but it is possible that the prolonged active hyperemia of excessive masturbation and coitus may also act as a cause. Upon gross examination the endometrium is distinctly thickened, and from it may project small polypoid masses. Histologically, there is hyperplasia of the interstitial tissue and of the glands. Certain observers distinguish an interstitial form and a glandular form of endometrial hyperplasia. This may be justified in a small number of the cases, but it is unusual that the predominance of fibrosis is constant throughout the endometrium of any given case. There may be infiltration of lymphoid and plasma cells and not infrequently areas of hemorrhage. This may be taken to indicate chronic inflammation, but whether primary or secondary is difficult to state. The hyperplasia of the glandular epithelium may be extensive, the cells often considerably elongated and sometimes thrown up into papillary projections into the acini. The glands may be large, irregular and more or less coiled. The hyperplasia may be so marked as to suggest adenomatous transformation, and it must be considered possible that the hyperplasia may be transformed gradually into tumorous growth. Clinical observation, however, shows that this does not often occur. The hyperplastic glands may project as polypoid masses into the cavity of the uterus. There is often great difficulty in distinguishing between this kind of glandular hyperplasia and that of the premenstrual endometrium. The criterion offered by Frankl is that in the premenstrual uterus the three layers of endometrium, compact, spongy and basal, are fairly well preserved, whereas in the hyperplastic endometrium this distinction is lost. Not infrequently there is an associated fibrosis of the myometrium, or myometrial hyperplasia. The functional disturbances include menorrhagia, metrorrhagia, dysmenorrhea and sterility, although certain cases are discovered in which no symptoms are produced.

Infectious Granulomata.—In generalized miliary tuberculosis, the endometrium or more rarely the myometrium may be affected. The usual manifestation, however, is an extension from tuberculous salpingitis. The tubercles form under or in the mucosa and may enlarge, fuse and slough to constitute caseous tuberculous endometritis. The process may extend into the myometrium by way of lymph or blood channels. Tuberculous perimetritis accompanies pelvic peritoneal tuberculosis. Syphilis affects the cervix more often than the fundus. Chancre may occur upon the cervix. Secondary mucous patches or papules not only occur, but by cicatrization may produce stenosis. Gummata in the cervix are usually small. A catarrhal endometritis which occurs in syphilis cannot be positively identified as of syphilitic origin. Actinomycosis sometimes extends from the neighborhood, especially the intestinal tract, to involve the uterus.

Tumors.—The most common benign tumor of the uterus is the fibroma. Adenofibromyoma is distinctly less frequent. Only rarely are other benign tumors, such as lipoma, lipomyoma, angioma and hemangio-endothe-

lioma reported. The most important malignant tumors are the squamous epithelioma of the cervix, the adenocarcinoma of the fundus, and the chorion-epithelioma. Rarely, however, sarcoma of the uterus is observed.

Fibromyoma.—This is the commonest tumor of the uterus and one of the most frequent in the entire body. Graves states that 20 per cent. of all women have fibromyoma, and that nearly all unmarried women after middle life have them. They are more frequent in the black than in the white race. They are frequently multiple, and there may be a diffuse fibromyomatosis of the uterus. According to their situation within the uterus they are spoken of as subserous, intramural, and submucous. The subserous or submucous fibromyomata may become pedunculated. In the order of frequency these tumors may be found in the posterior, anterior or lateral walls, and in about 10 per cent. of the cases in the cervix. Similar tumors are encountered in the Fallopian tubes, the broad ligaments, the round ligaments, the ovary, the vagina and other parts of the urogenital tract. The fibromyoma is either a smooth, spheroidal or an irregular, nodular mass. In the earlier stages it is not sharply defined from the surrounding tissue, but as it grows older it becomes definitely encapsulated and may be easily shelled out. It is ordinarily firmer in consistence than the uterine muscle, and with increasing growth of connective tissue may become very dense and hard, the *fibroma durum*. Secondary changes, particularly edema, may give it a soft consistency, the *fibroma molle*. It is usually a pale pink color but with increasing fibrous tissue becomes a glossy,

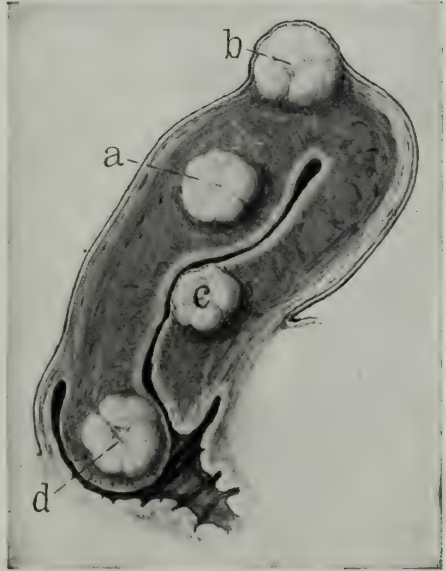


FIG. 351.—Schematic longitudinal sagittal section of uterus, showing various positions of fibromyomata; a, intramural; b, subperitoneal; c, submucous; d, cervical. From *Gynecology*, by B. M. Anspach.

light gray color. It cuts with considerable resistance and usually bulges markedly above the softer surrounding uterine tissue. The cut surface is moderately moist but may be edematous, and shows a very characteristic whorling of muscle and connective tissue bands, which gives it the so-called "watered silk" appearance. Microscopically, the essential cell is the smooth muscle cell with its long spindle form body and long nucleus with rounded ends. In the earlier stages this constitutes practically the entire tumor, but subsequently connective tissue cells and fibrils appear in greater number until finally they constitute the larger part of the tumor. Supporting the whorled muscle and connective tissue cells, which may be cut longitudinally, obliquely and transversely, there are fairly definite bands of connective tissue with blood and lymph vessels. The blood vessels ramify through the tumor mass and in their finer divisions may have extremely thin walls. In addition, there may

be gland spaces and acini, often tubular in character and sometimes dilated to form small cysts. This constitutes the so-called adenofibromyoma. According to McCarty and Blackman such glandular spaces are found in 6.5 per cent. of all these tumors. Unless the glandular spaces are large enough, or present in sufficient numbers to produce small areas of spongy character in the cut surface, this tumor does not differ grossly from the fibromyoma. The origin of the uterine fibromyoma has been extensively discussed without satisfactory conclusion. Unsatisfied sexual excitement, and sexual abstinence cannot be regarded as causative without further evidence. Many investigators refer the condition to some disturbance during embryonal development. This may be the result of embryonal misplacement of fragments of the Müllerian



FIG. 352—Interstitial fibromyoma which has undergone necrosis and cyst formation. From *Gynecology*, by B. M. Anspach.

duct, or because of the fact that in some instances the tumor appears to take origin from blood vessels, is ascribed to irregularity in interrelationship of development of Müllerian ducts and the vascular system. According to Ewing, the adenomatous portion of the adenomyoma may be ascribed to embryonal misplacement of remnants of Müllerian ducts, mesonephros, Wolffian ducts or peritoneum. Some of the adenomyofibromas, especially those situated near the uterine serosa, are probably developed from adult endometrial fragments which pass through the tube and lodge upon the peritoneum. These are discussed in the section on ovaries.

The uterine fibromyoma is subject to a variety of secondary changes. Thus, owing to vascular disturbance which may occur, especially from malposition of the uterus, there may be edema which sometimes is so great as to produce cysts within the tumor. As a sequence of edema, or perhaps inde-

pendently, mucoid may accumulate and lend a myxomatous character. Fatty degeneration is common in the smooth muscle and may affect other parts as well. If the circulation be obliterated, necrosis may produce softening of the entire tumor but more commonly it is present in small areas. Calcification may occur in foci within the tumor and may also form within the denser part in and near the capsule. More especially in the submucous tumors, inflammation is likely to occur and in the same situation gangrene sometimes ensues. Dilatation of lymphatics and of blood vessels may give rise to lymphangiectatic or hemangiectatic fibromyoma.

Of especial importance in connection with secondary changes in the fibromyoma, is the occurrence of sarcomatous change which is said to be observed in about one per cent. of all cases. As far as widespread invasion and obvious malignancy are concerned, this figure is too high since it comprises a group of tumors in which the evidence of malignant change is only in microscopic fields. The grossly invasive tumors extend through the wall of the uterus to neighboring structures, involve lymphatics and ultimately metastasize by the blood stream to lungs and other viscera. The histologic changes include an increased vascularity of the tumor, variation in size and staining character of cells and nuclei, multinucleated cells, irregular mitoses, and more or less characteristic vascularization in which the wall of the vessel is made up of tumor cells. When malignancy is established, it is impossible to say whether the cells originated from the smooth muscle to constitute a leiomyosarcoma, or from connective tissue to constitute a spindle cell sarcoma, or are derived from both.

The most common functional changes incident to leiomyofibroma are menorrhagia and metrorrhagia. The condition apparently predisposes to, if it does not actually excite, uterine endometrial hyperplasia. Uterine malposition, especially retroversion, and even prolapse, may be caused by fibromyoma. The tumor also apparently acts as one of the predisposing causes of carcinoma. Impaction of large masses of tumor in the pelvis may produce pressure symptoms, particularly of the rectum, with constipation, and of the ureters, with damming back of the urine into ureters and renal pelvis.

Although a certain proportion of victims of the uterine fibromyoma are sterile, conception frequently occurs. Although abortion or miscarriage may ensue, pregnancy may go to term and may be uneventful. Nevertheless, serious complications of pregnancy and labor may result from the position or size of the tumors. Fibromyomata may enlarge during pregnancy and sometimes may disappear after childbirth.

Squamous Epithelioma.—This is one of the most common of all cancers. While it may occur at any time of life, it is more frequently a disease of late middle life, affecting particularly multipara and those who have had cervical lacerations or erosions. It may originate as a small, firm, lump in the cervix, or as an ulcer, which may extend by erosion or by infiltration. It extends into the cervix fairly rapidly and produces early lymphatic metastasis in the parametrial tissues. Extension to the body of the uterus is by no means frequent.

Grossly, the tumor may appear as an indurated infiltrating ulcer with a somewhat necrotic base, as an extensive ulceration with shaggy, gray necrotic or bleeding base and everted edges, and only rarely as a fungating or projecting polypoid or cauliflower-like mass. In the more advanced cases infection may play a prominent part, and often saprophytic invasion produces a foul smelling discolored mass. Discharge from the vagina may be mucous, mucopurulent, bloody or gangrenous. Cross section of the uterus usually shows the tumor to be a fairly firm, gray mass with or without foci of hemorrhage and necrosis. Its margins as a rule are irregular but fairly well delimited. Microscopically, the picture is usually that of fairly large nests of cells, the outer members being of basal character and the inner members somewhat differentiated



FIG. 353—Advanced squamous epithelioma of the cervix. The vaginal cervix has been destroyed by the tumor which has reached the internal os. From *Gynecology*, by B. M. Anspach.

toward intermediate cells. The central parts often consist of more or less necrotic cells with pyknotic and fragmented nuclei. Lymphoid infiltration is extremely common and in many cases there are considerable numbers of eosinophiles. Not infrequently polymorphonuclears infiltrate in considerable quantities and there may be small foci resembling abscesses. In some cases there is actual differentiation of cells to form prickly cells and squamous cells, but keratinization and pearl formation are not especially frequent. Metastasis occurs early into the parametrial tissues and thence may be widespread through the lymphatic system. It is unusual, however, for the superficial lymph nodes of the groin to be involved.

Squamous epithelioma is also seen rather rarely in the fundus of the uterus. In most of the cases this is apparently a metaplasia of the epithelium of an

adenocarcinoma, but it is possible that metaplasia may have occurred in the precancerous lesion, or squamous epithelium be present because of a fault of embryonal development.

Adenocarcinoma arises especially in the endometrium of the fundus. It may develop upon a preëxisting endometrial hyperplasia or without any preceding history of disturbance. The fairly frequent association of myoma with adenocarcinoma of the uterus is probably due to the fact that the former leads to an endometrial hyperplasia, which subsequently becomes tumorous. This tumor occurs in somewhat later life than does the cancer of the cervix, grows less rapidly and metastasizes later. In the forty-four tumors studied by Meigs only four showed metastasis. It may be a focal area usually high in the fundus or a diffuse adenocarcinomatosis of the endometrium. Its first growth is apparently into the cavity of the uterus in the form either of a somewhat roughened, solid mass of soft, proliferated mucosa, or as multiple papillæ. It then slowly infiltrates the muscle and may eventually occupy a large area in the muscle and penetrate through into the peritoneum. Histologically, it is usually an undoubted adenocarcinoma with markedly enlarged, irregular glands or acini, lined by multiple



FIG. 354—Early adenocarcinoma of fundus. From Gynecology, by B. M. Anspach.

layers of epithelial cells, of variable size and with hyperchromatic nuclei and mitotic figures. In association with the acini there are often solid masses of epithelium penetrating through lymphatic spaces. Inflammation is not so common in adenocarcinoma of the fundus as in the carcinoma of the cervix, and the tumor may attain considerable size with relatively little necrosis. In some cases dedifferentiation progresses and the tumor is a carcinoma simplex. As has been mentioned above, a small number of cases may show metaplasia with the formation of stratified squamous epithelium and pearls. Lymphatic extension, when it occurs, is along the lymphatics accompanying the tubes, and the tumor is not so likely to show early parametrial metastases as is the carcinoma of the cervix. In some cases, however, blood stream metastasis occurs to the liver and other organs.

Adenocarcinoma may also originate from the glands of the cervix and perhaps also from the columnar epithelium covering erosions. In the cervical adenocarcinoma the acini resemble more nearly the simple mucous glands of the cervix. It is only rarely, however, that a mucoid carcinoma is observed. Metastasis and extension of these tumors resembles that of the cervical squamous epithelioma. The topic of cancer of the uterus is admirably covered by Cullen.

Chorionepithelioma.—Although this may occur at any time after sexual maturity, it is usually a tumor of multipara after the fortieth year. The tumor develops three or four months after delivery of a hydatidiform mole, or less frequently after abortion, miscarriage or normal pregnancy. It may, however, occur very soon after any of these events or be much delayed. The tumor is derived from the covering cells of the chorionic villi and is thus made up of the cuboidal cells of Langhans and the syncytium. The cells are therefore trophoblastic and are genetically ectoblastic epithelium. The tumor usually begins as a relatively small nodule in the fundus of the uterus, and enlarges by growth into the cavity and extension through the endometrium into the uterine wall. It is a soft, bulging, irregular mass, only rarely papillary in character. It is usually red because of rich vascularization, and undergoes necrosis early in its course. Cross section shows definite penetration of the mass into the uterine wall. Histologically, it shows irregular masses of cuboidal cells with small vesicular or solid nuclei and finely granular or somewhat vesicular edematous cytoplasm which contains glycogen. Intermingled with these cells are multinucleated cell masses representing the chorionic syncytium. The cytoplasm of the multinucleated cell masses is usually vesicular and may contain much fat, but the nuclei are usually dense rather than vesicular. Mitotic figures are more common in the cuboidal than in the multinucleated cells. The blood vessels are numerous and often cavernous, and the larger spaces often contain masses of tumor cells. The rich vascularization is responsible for bleeding, which occurs comparatively early in the course of the disease, so that early diagnosis is made, and cure by excision of the uterus is by no means infrequent. On the other hand, invasion of the vessels is early so that secondary nodules appear in various parts of the body. As has been mentioned, cell masses of chorion or of tumor may be transported to the vagina and give rise on the one hand to primary chorionepithelioma in this situation or on the other hand to metastases of the primary uterine tumor. Distant metastasis is more commonly to the lungs but may appear in other viscera including the heart.

The chorionepithelioma is to be distinguished from the malignant hydatidiform mole or chorio-adenoma. The majority of the hydatidiform moles are strictly benign and after they are delivered no further consequences occur. Nevertheless, the mole as a whole may become invasive, in which case penetration of the endometrium and of the muscularis occurs, participated in by the connective tissue of the mole as well as the covering epithelium. The degree of epithelial proliferation, however, is distinctly less marked than in the

case of chorionepithelioma. Destruction and penetration of the uterus may occur but distant metastasis is rare.

Sarcoma.—It is probable that the most frequent sarcoma of the uterus is that which originates in the fibromyoma, and may be considered either as a myosarcoma or as a spindle cell sarcoma. Rarely, sarcoma develops in the endometrium as a nodular mass which grows rapidly, bleeds freely and may project into the uterine cavity in polypoid or papillary form. It may be of spindle cell variety but round cell tumors are also described. In the latter, however, it is extremely difficult to demonstrate that the round cells are not of epithelial origin. Occasionally, a mixture of carcinoma and sarcoma is described, but it is often difficult to exclude non-malignant irritative proliferation of the glands as the presumed carcinomatous condition in this combination.

FIG. 355

FIG. 356



FIG. 355—The normal position of the uterus, A; extreme anteversion, B; and retroversion, C. The uterus remains anteфлекed in all. The directions of intra-abdominal pressure is indicated by the arrows.

FIG. 356—Retroversion and retroflexion of uterus in the figure with broken lines. From Gynecology, by B. M. Anspach.

It is of course possible that carcinoma and sarcoma may arise independently and subsequently mingle. The third form of sarcoma is the sarcoma botryoides, a mixed tumor of invasive character found most commonly in the cervix but occurring also in rare instances in the fundus, described more fully in the discussion of vagina. The sarcomata as a group are likely to extend into the parametrial tissue and lymph nodes as well as produce widespread metastasis through the blood stream. Endothelioma is also described in the uterus, but a positive diagnosis is only made with the greatest difficulty because of the resemblance of endothelium to epithelium.

Alterations of Position.—The uterus normally lies almost horizontally over the bladder and practically at right angles to the vaginal axis. When the uterine axis is angulated within the uterus beyond the normal degree, it is the seat of various forms of flexion. When the whole uterine axis is out of normal position it exhibits various forms of version. Retroversion occurs in three degrees, the first in which there is a backward elevation of the axis so

that the uterus assumes a more vertical position, the second in which the uterine axis is in line with that of the vagina, and the third in which the axis is posterior to that of the vagina and usually bent so as to have a retroflexion. The uterus is normally in a position of anteversion and anteflexion and it is only rarely that the former exceeds the normal degree. Hyperanteflexion, however, is sometimes observed. Lateroversion and lateroflexion are not common except in severe lesions of the pelvis. Anteposition and retrocession indicate that the whole uterus is either forward of, or posterior to, the normal situation. Prolapse indicates descent of the uterus as far as the vaginal outlet; when it projects beyond the outlet it is the seat of procidentia. This may be accompanied by partial or complete inversion. The most common cause of uterine displacements, more particularly retroversion and prolapse or procidentia, is injury to the supporting muscles and fascias in labor. Retroversion, however, may occur in nullipara because of failure of support due to the so-called lax habitus. Other causes include especially the action of tumors, either by weight or destruction of tissues, and the traction of adhesions.

The lumen may be narrowed or occluded by tumors, cicatrices, internal adhesions or by congenital faults. Behind obstructions, fluids may accumulate; if blood, to constitute hematometra; if pus, to constitute pyometra; if uterine secretion, which frequently becomes serous in character, to constitute hydrometra.

THE PLACENTA

Anomalies of the placenta include placenta diparita, triparita, etc., in which the placenta shows segmentation, placenta duplex, triplex, etc., in which the placenta is completely divided into two or more parts, placenta arcuata, the horseshoe form, and other variations from the normal. Eccentric attachment of the cord is not uncommon.

Retrogressive Processes.—These include cloudy swelling, fatty degeneration, hyalien necrosis and calcification. The last occurs in smaller or larger areas of necrosis and is often of no significance.

Circulatory Disturbances.—Various forms of interruption of venous drainage may produce passive hyperemia which is usually present only in foci. Edema is not uncommon. Many cases are without known cause but some are due to maternal nephritis. Thrombosis may occur in maternal or fetal circulation.

The so-called infarcts of the placenta may be well circumscribed red masses of coagulated blood with slight tissue necrosis, or pale yellow, decolorized masses of necrotic blood and placental tissue. They are somewhat more frequent in toxic than in non-toxic pregnancies but are probably a sequence rather than a cause of toxemia. That they are due to vascular occlusion is not necessarily true of all cases. Whether they are due to disturbance of either the fetal or the maternal circulation, without involvement of the other, is not known. Frazer's injection experiments indicate that occlusion of fetal circulation would be sufficient to produce such a lesion. Adair summarizes the causes as endarteritis, periarteritis, and thrombosis and localized hemorrhages,

which may result from static, traumatic or toxic conditions. It is probable that infection and inflammation play a part in only a small number of the cases. Hemorrhage or uteroplacental apoplexy is referred to in discussing abnormal attachment of the placenta.

Inflammation.—With the exception of that due to infection of the placenta retained after birth, inflammation is unusual. Infection, however, may be transmitted from decidua to placenta, or rarely there may be metastatic abscess in the placenta.

Infectious Granulomata.—Tuberculosis of the placenta is not common. The bacilli are deposited from the maternal blood in the intervillous spaces from which, probably subsequent to thrombosis, the process penetrates the villi to set up miliary tubercles, often poor in giant cells, or larger conglomerate tuberculous masses.

In many cases where syphilitic fetuses are born, the placenta shows no abnormality. The most significant finding is a large hyperplastic placenta and a small fetus. The large, pale placenta shows enlarged villi in which there is overgrowth of connective tissue and moderate edema. Gumma is extremely rare and it is unusual to find any marked lymphoid infiltration. Peri- and endovasculitis are common but by no means diagnostic. Infarcts occur in about one-third of the cases (Mönckeberg and Aviles). In fact any of the changes described may occur in non-syphilitic, chronic inflammations of the placenta. Spirochetes are not often found. Apparently, the placenta permits free passage of spirochetes but is not a favorable place for their growth.

Hydatidiform Mole.—This occurs in older multipara more often than in primipara. It is to be regarded as a hyperplasia rather than a tumor. The villi are enlarged to constitute pale, soft, translucent, more or less pedunculated, grape-like masses varying in size from a few millimeters to a centimeter or more. Histologically, the villi are the seat of marked edema, often with compression or disappearance of capillaries. The trophoblastic epithelium may be normal or more often shows focal increases in the number of cuboidal cells and increase in mass of the syncytium with vacuolization of the cytoplasm. Probably most moles originate from the chorion frondosum but a few may originate from the chorion laeve. Usually there is no remnant of embryo or fetus but in a few cases development may be advanced. They may produce symptoms resembling the toxemias of pregnancy (Brodhead and Kassebohm). The relation to chorio-adenoma and chorionepithelioma has been discussed with uterus.

Tumors.—Aside from those just mentioned, there remains principally the angioma which may be localized or extensive in the form of angioma, fibroangioma or cavernous angioma.

Cysts may originate in amnion, vitelline duct, allantois, chorionic villi or may occur as hemorrhagic pseudocysts in the placenta.

Abnormalities of Attachment.—Ordinarily the placenta is attached to or near the fundus, but may be attached at the side near the cervical portion or completely cover the internal os, placenta previa. Sometimes the placenta is of ring form or crescent form and is attached to the uterine wall without inter-

vening decidua, and is probably due to absence of endometrium at the point because of previous inflammation and cicatrization.

More especially when the placenta is abnormally placed, but also when in normal position, it may be detached (ablatio) with accompanying hemorrhage. In placenta previa, this uteroplacental apoplexy is due to mechanical causes.



FIG. 357—Hydatidiform mole. From Gynecology, by B. M. Anspach.

but in placenta previa as well as in normally situated placentæ, it may be due, according to Holmes, to traumatism, to pathological changes in the uteroplacental junction such as infarction or inflammation, or to toxemia of renal or eclamptic nature.

THE FALLOPIAN TUBES

Circulatory Disturbances.—Passive hyperemia occurs as the result of general diseases such as heart disease, or of local conditions which may obstruct

outflow of blood, such as malposition of the uterus or torsion of the tubes. Hemorrhagic infarcts may also result from torsion. Hemorrhage may be due to passive hyperemia, inflammations and extra-uterine pregnancy. The tube may take part in menstruation. Hematosalpinx occurs in tubes obstructed at the fimbriated or at both ends and is principally due to menstrual blood originating in the tube or infiltrating from the uterus.

Inflammation.—Exposure to cold or other vague causes may bring about acute hyperemia of the tubes which may be painful, but such things do not cause inflammation. It is now believed that acute salpingitis is invariably due to bacteria. In the majority of instances the infection travels by way of the uterine mucosa and is due to the gonococcus. The gonococcus was the cause in 80 per cent. of the cases studied by Gurd. In a number of cases of puerperal acute endometritis the tubes are also involved, but the infection is spread by way of the lymphatics from uterus to tubes. Infection may enter the fimbriated end from a peritonitis, may attack the peritoneal surface when invading from appendicitis or may be blood borne in septicemias or pyemias.

Acute gonorrheal salpingitis is usually catarrhal at first and then becomes more or less purulent. The tubes are hyperemic, swollen, elongated, tense, tender and painful. The mucosa is swollen and is covered with catarrhal or mucopurulent exudate, which may leak through the fimbriated extremity and produce a mild fibrinous peritonitis, practically always confined to the pelvis. Microscopically, the epithelium is swollen, degenerate and non-ciliated. Often there is extensive desquamation and ulceration, the ulcers sometimes covered with a small amount of fibrin. The underlying connective tissues are infiltrated with lymphoid, endothelial and eosinophilic cells and, in most cases but not always, enormous numbers of plasma cells. If the case be recent, the pus shows the usual intracellular gram-negative diplococci, but in later stages the pus is quite sterile. The inflammation may extend through the entire wall of the tube and even into the parametrial tissues.

Acute suppurative or septic salpingitis most commonly is secondary to puerperal endometritis and metritis. Because of lymphatic transmission of the infection the lesion begins within the tubal wall and then involves the entire structure. Hyperemia, edema, suppuration, necrosis and ulceration constitute the changes. Mild cases may show less cellular infiltration; more severe cases may become phlegmonous.

Acute salpingitis of any form may become quiescent and heal. The septic forms, however, are likely to be fatal because of the accompanying widespread infection. Gonorrheal salpingitis is likely to become converted into a chronic inflammation, although some cases cease to progress and the fibrosis is then to be regarded as cicatrization. Within the tube the diffuse inflammation is followed by fibrosis, the destroyed epithelium is only partly replaced, the villi are short and adherent, the internal adhesions may be so constituted as to produce cysts, the epithelium may grow into the surrounding tissues to produce small papillary cysts, and the lymphoid and plasma cell infiltrates may remain over long periods of time. The local peritonitis produces adhesions

between tubes and ovaries, bladder, rectum, intestine and appendix, and may lead to a dense matting together of all the pelvic viscera. Contraction of adhesions about the tubes may produce tortuosity and marked deformity.

The adhesion of plicæ within the tubes may produce complete occlusion, especially at the uterine end; the adhesions of fimbriæ may close the fimbriated extremity. If the acute inflammation persist, pus accumulates in the tube, dilates it and forms pyosalpinx. The ampulla is most widely dilated. Adhesions of the peritoneum, scar-like bands of tissue on the outer surface, or adhesion within the tube may divide the accumulated contents into saccular areas, a pyosalpinx saccata. The pus may become inspissated into a cheesy mass, not to be confused with tuberculosis, or may become calcified. It probably only rarely liquefies to form a limpid serous fluid. Provided suppura-

tion subside, the accumulation of secretion may dilate the tube in even greater degree to form hydrosalpinx or in the sacculated forms sactosalpinx serosa. The pyosalpinx is usually lined by more or less chronic granulation tissue; the hydrosalpinx is lined by flattened columnar epithelium without cilia. The walls show the changes noted above, but in hydrosalpinx extreme dilatation may thin the walls so that they are merely a mass of dense connective tissue from which muscle has disap-

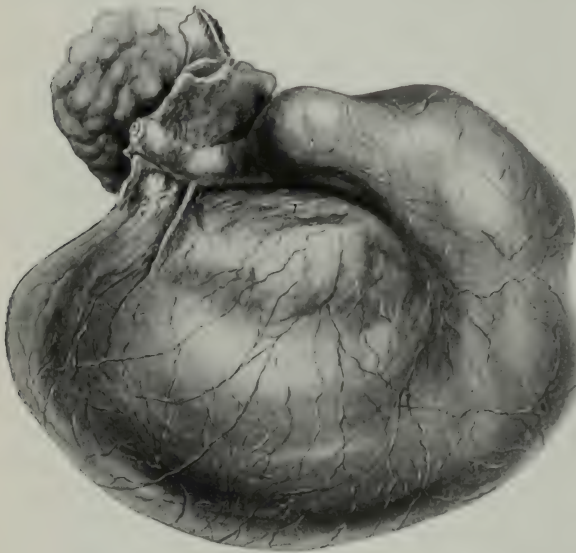


FIG. 358—Hydrosalpinx

peared. Occasionally gonorrheal salpingitis may heal and leave only a mass of chronic inflammatory or cicatricial connective tissue at the uterine end, salpingitis isthmica nodosa. Similar multiple nodules give rise to the name salpingitis nodosa.

The fimbriæ may, instead of fusing together, become adherent to the ovary. Accumulations of pus in this situation form the tubo-ovarian abscess. The inflammation may finally penetrate through the albuginea into the ovarian tissue. The nature of tubo-ovarian cyst is the subject of some question. It may possibly be like a localized hydrosalpinx but is probably more commonly produced by rupture of an ovarian cyst into the area of adhesion.

Infectious Granulomata.—Tuberculosis is common and is usually bilateral. It may be a tuberculous perisalpingitis, as a part of tuberculous peritonitis, in which the wall is studded with miliary or small conglomerate tubercles. The process may extend thence into the substance of the tubes. In our

experience, it also occurs frequently as miliary tubercles in the mucous and muscular coats in association with a chronic salpingitis. It may affect principally the mucosa. Involving muscularis or mucosa, the process may advance with extensive caseation, not infrequently complicated by mixed infection. Syphilis is only rarely observed and then in the form of gumma. Actinomycosis is usually an extension from the neighborhood, especially from the intestine.

Tumors.—These are unusual in the tubes. Fibroma, fibromyoma, and angioma are reported. Adenoma may occur but should not be confused with hyperplasia of epithelium such as occurs in chronic salpingitis. Adenofibroma is probably in most cases the implantation tumor of Sampson described with diseases of the ovary, or may be due to faults in embryonal development of the Müllerian duct. Although adenocarcinoma may occur, the usual carcinoma is a papillary carcinoma which may penetrate into and widely invade the peritoneum. Lymphatic metastasis may occur in lymph nodes, ovaries and uterus. Sarcoma is extremely rare. Secondary tumors originate in ovary, uterus and neighboring organs or may extend from the peritoneum.

Extra-uterine Pregnancy.—Although impregnation of the ovum occurs normally in the Fallopian tube, the ovum descends into the uterus before it embeds itself and pregnancy proceeds. Nevertheless, it is not rare for the ovum to implant itself within the Fallopian tube and indeed this may occur in the tubo-ovarian junction, in the ovary and in the peritoneum. In most cases of tubal pregnancy there is found a preëxisting chronic disease which produces tortuosity, elongation, or sacculation of the tube so that the passage of the ovum through the tube is delayed. Nevertheless, the condition sometimes occurs in an otherwise normal tube. Attachment in the tubo-ovarian junction is practically always in connection with chronic adhesive disease. Implantation in the ovary may be due to the same condition, or, apparently can occur by the impregnation of the ovum within the mature Graafian follicle. Implantation in the peritoneum may be primary, but is usually due to dislodgment of an ovum already implanted near or in the fimbriated extremity of the tube. Decidua may be formed at the site of extra-uterine pregnancies, but is almost always present in the uterus also.

Tubal pregnancy usually occurs in the outer third of the tube. The ovum penetrates the lining epithelium and attaches itself to the underlying connective tissue and often burrows into the muscular layer. The trophoblast and the earlier stages of the embryo develop normally. The blood vessels of the surrounding parts undergo marked dilatation and supply blood for the developing ovum. Decidual reaction is not uncommon. The patient exhibits all the signs of pregnancy except the gradually enlarging uterus. The tube enlarges at the site of implantation, becomes tense and hyperemic. Usually the pregnancy is interrupted before the third month. In about one-fourth of the cases the tube ruptures, hemorrhage occurs, which may be profound and even fatal, and the embryo is dislodged into the peritoneum and dies. More often, however, the membranes rupture within the tube and tubal abortion is said to have occurred. The incident hemorrhage may be confined to that

segment of the tube and constitute hematocele. If the blood does not clot, hemorrhage, sometimes severe, may occur through the fimbriated extremities. Most cases are terminated by surgical intervention because of pain, hemorrhage or both. In others, however, the embryo dies and the whole mass of membrane, embryo and hemorrhage, if it has occurred, is organized and cicatrized.

THE OVARY

Circulatory Disturbances.—Passive hyperemia may be due to general circulatory diseases or may be the result of local interference with drainage of the blood such as occurs in malposition of the ovary, malposition of the pelvic viscera, or torsion of the ovary upon a pedicle. Edema is usually associated with the passive hyperemia. The ovary may be distinctly anemic because of pressure upon it by tumors in the pelvis. Usually prolongation of the anemia and pressure is followed by atrophy.

Hemorrhage in the ovary is fairly common, originating in the Graafian follicle or at some stage following its rupture. The hemorrhage incident to rupture may be severe and lead to collapse. Bleeding may occur into a corpus luteum, more frequently that of pregnancy than the ordinary menstrual corpus luteum, and produce ovarian hematocele. Occasionally, the rupture of vessels in the margin of the corpus luteum may produce diffuse hemorrhage throughout the ovary. Diffuse hemorrhage, however, is much more unusual under any circumstances than is focal hemorrhage. It may accompany a general hemorrhagic infection and other disease or may be due to twisting of the pedicle of an enlarged ovary.

Inflammation.—Acute inflammations of the ovary are not frequent. Many of the conditions formerly supposed to represent chronic inflammation are now looked upon as either cystic disease of non-inflammatory origin, the cicatrization of an old inflammatory process, or are merely atrophy due either to preëxisting disease or to age. Acute oöphoritis may be due to infection either through the lymphatics or by direct invasion from primary suppurative processes in the uterus, the Fallopian tubes, the parametrium, the appendix or the peritoneum. It may be hematogenous in cases of pyemia and septicemia or may be carried to the organ from cryptic foci of infection. Acute inflammation, presumably of metastatic character, occurs in the course of mumps but is less frequent in the ovary than in the testis. Similar lesions may accompany diphtheria and measles, scarlet fever and typhoid fever. Gonococcus infection may spread from the tube and affect the surface of the ovary in an acute peri-oöphoritis. Frankl maintains, however, that not only is this true, but that frequently the gonococci invade the substance of the ovary to produce acute, diffuse and even suppurative inflammation. He regards gonorrhea as an important cause of acute oöphoritis. If, however, abscess be formed it is probably due to the ascent of other organisms through the uterus and tubes and parametrium.

Acute oöphoritis may be present as a diffuse acute seropurulent process or as abscess. The organ is enlarged, tense, somewhat fluctuant and of pink

color. It cuts easily and the cut surface is smooth, usually quite moist, and from it may be expressed a seropurulent exudate. Histologically, there is severe hyperemia, marked edema and infiltration of lymphoid and plasma cells and polymorphonuclear leucocytes. In those forms accompanying such conditions as puerperal sepsis, the polymorphonuclear leucocytes are in abundance. In the form due to gonococcus there is usually an abundance of plasma cells. If abscess supervene, the features are grossly and microscopically about the same as those observed elsewhere, except that as the abscess becomes older the marginal zone of granulation tissue may show a distinct yellow line. Microscopically, this appearance is found to be due to large, finely vacuolated cells resembling those of the corpus luteum. They are, however, cells of endothelial type, probably phagocytic for fatty and lipid materials rather than true cells of the corpus luteum. As acute inflammation subsides, there is a proliferation of granulation tissue with subsequent cicatrization and marked atrophy of the organ.

Infectious Granulomata.—Tuberculosis is by no means uncommon in the ovary. It may extend from tuberculous peritonitis in the neighborhood or may be transmitted by blood or lymphatic stream. When extending from tuberculous peritonitis the process rapidly involves the ovary itself. The lesions may be miliary or may be conglomerate with extensive caseation. Diseased and cystic ovaries are not exempt from tuberculous infection. The only important manifestation of syphilis is the gumma. Actinomycosis may spread to the ovary from lesions in the neighborhood.

Retention Cysts.—The ovary is subject to cystic disease in various forms. Some cysts are proliferative in nature and are justifiably classed with tumors. The others included in this section, are not proliferative although the ovary may be riddled with them. By some authors they are called non-proliferative tumors, a nomenclature which is totally unjustified. The term retention cyst is employed with the primary understanding that the fluid retained is in no sense a secretion that otherwise would be poured out of the organ. The fluid is formed as the result perhaps of passive hyperemia, irritation, secretion by lining cells, or attraction on the part of necrotic material within the space, but the mechanism is not clearly understood. Such cysts may be formed at any stage of development of the Graafian follicle, the corpus luteum or the corpus fibrosum.

Follicular cysts are those which originate in the Graafian follicles. It is well known that many follicles do not mature. Ordinarily they undergo complete organization and atresia. Even normally some become small cysts. The conditions which cause large numbers to become cystic are not known, although passive and repeated active hyperemia and fibrosis of the organ appear to have some influence. In the less severe instances, the ovary is moderately enlarged and shows on both the outer and cut surfaces large numbers of thin walled monocular cysts containing clear, colorless or amber fluid. The fluid may become viscid by inspissation or be converted into a semi-solid hyaline mass. Microscopically, the small cysts are lined by remnants of

the stratum granulosum. In the course of the disease one or two cysts may enlarge to diameters of twenty or thirty centimeters or more. They are usually also monolocular and contain the same type of fluid, but the lining cells have disappeared or may occasionally be represented by small wart-like excrescences.

Corpus luteum cysts are usually single and only occasionally attain large size. The cyst wall shows a fairly thick convoluted yellow line resembling that of the corpus luteum. Microscopically, the convoluted masses of lutein cells are found. The fluid is usually cloudy, limpid, but of dark or reddish-yellow color. When the cyst enlarges the lining layer becomes less distinct and may disappear. Then the distinction between this type and follicular cysts cannot be certain. If the cyst originate during the hemorrhagic stage of the corpus, the lutein cells may be covered by a layer of connective tissue with a few granules of blood pigment.

Theca-lutein cysts are usually small and may be multiple. They probably originate in follicles. The lining is of connective tissue cells of the theca interna, which undergo hyperplasia and take up lutein pigment. The cell mass, however, does not show the convolutions of the corpus luteum. Theca-lutein cysts are the especial accompaniment of hydatidiform mole and chorionepithelioma. Frankl states that in from 50 to 63 per cent. of the cases of chorionepithelioma, cystic disease of the ovary was present, and that in practically all of the instances the cysts were theca-lutein cysts.

Tumors.—Many of the benign tumors of the ovary tend to become malignant and to show stages in which diagnosis is difficult. Fibroma, fibromyoma and solid adenoma occur. Of greater frequency, however, are the forms of cystadenoma, a proliferative cystic disease, progressive in course and capable of malignant change. Although by the names employed for the two forms, pseudomucinous cystadenoma and serous cystadenoma, the cyst content would seem to be a differential feature, there are other points of difference.

Pseudomucinous Cystadenoma.—This is the most frequent tumor of the ovary. The tumor almost or completely replaces the ovary. It is more commonly unilateral and as a rule is pedunculated but may grow in the broad ligament (intraligamentary). The cystic mass is encapsulated, oval in shape, with a smooth, glossy, somewhat lobulated surface and is multilocular. The loculi are variable in size and more especially with the larger ones have thin walls. The content is primarily a viscid fluid, principally pseudomucin. This differs from mucin in that it takes acid stains and although soluble in dilute alkalies is not precipitated by weak acids. It contains a copper reducing body, probably mucoitin-sulphuric acid (Levene). It is a pale yellow fluid which may be discolored by secondary changes as necrosis or hemorrhage. The pseudomucin may by inspissation become semisolid or solid and when brown in color resembles colloid but does not contain iodine. Old cysts may contain cholesterol crystals. Microscopically, the material, whether viscid or solid, takes the acid stain and is either granular, thready or homogeneous. The cysts are lined with a single layer of nonciliated columnar cells with dense basal nuclei, and are often goblet cells because of accumulation of the pseudomucin

which they secrete. They are supported on a connective tissue framework only moderately well vascularized. They may be flattened by pressure of fluid in the cyst. Epithelial proliferation into the cyst cavity forms papillæ which may be large and extensive. Proliferation into the connective tissue produces acinar spaces or adenoma. Either type of proliferation may become malignant.

Rupture into the peritoneum may lead to pseudomyxoma peritonei. The pseudomucin is taken up by peritoneal lymphatics and may accumulate to

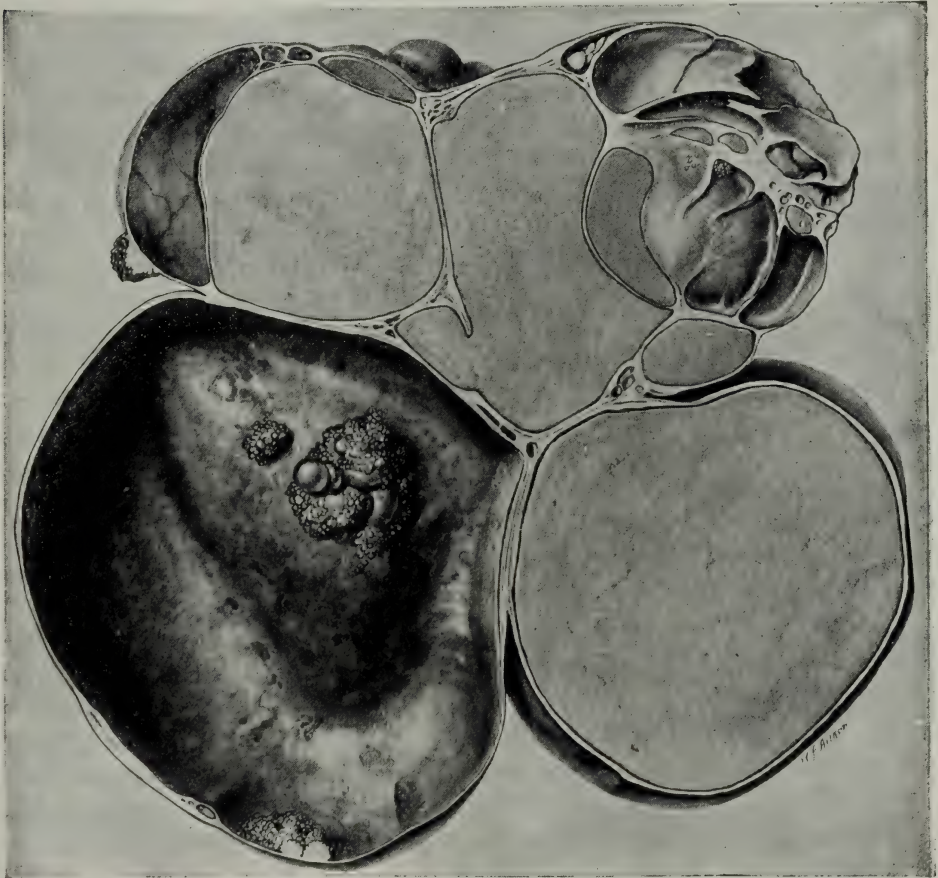


FIG. 359—Serous cystadenoma of ovary with papilla formation. From Gynecology, by B. M. Anspach.

form grape-like cystic projections from the peritoneum. These are lymphatic cysts and are not lined by epithelium. The pseudomucin may remain free in the peritoneal cavity. In either case extensive adhesions are likely to form which may ultimately produce intestinal obstruction. Only rarely are the tumor cells implanted upon the peritoneum to set up new cystic or papillary tumors.

The origin of this tumor is not definitely established. Some believe that it originates in follicles and others regard it as a one-sided development of the totipotential teratoma.

Serous Cystadenoma.—This is not so common but is more frequently bilateral than the pseudomucinous form. It usually does not exceed a diameter

of eighteen or twenty centimeters. It is more often intraligamentary than pedunculated. Upon gross examination it is often apparently monolocular with thick walls, but as a rule, further examination shows numerous minute additional cysts in the walls. It contains a thin serous fluid rich in protein but devoid of pseudomucin. It is lined by low columnar epithelium covered with cilia and with centrally placed nuclei. The cilia are best seen by examining cells scraped off the fresh surface and placed in warm salt solution. Proliferation may occur into the wall to produce adenoma, but much more frequent and striking is the disposition to proliferate internally and produce extensive papillary growth. The tumor is almost constantly a papilliferous cystadenoma. The papillæ are intricately branched, are covered by the



FIG. 360—Endometrioma from posterior vaginal wall (patient of W. H. Weir, M.D.).

ciliated columnar cells and may fill the entire cavity. In large cysts under pressure or in peritoneal growths the cilia often disappear. It is not uncommon for the epithelial masses to grow through the cyst wall and produce papilloma on the peritoneal surface. Either from rupture of the cyst, accidental spilling of the contents during operation, or most frequently by detachment of cells from the extracystic papilloma, the process may be implanted widely upon the peritoneum. The secretion continues and most marked ascites is produced. Even extensive papillary growth may not be histologically invasive, but ultimately in nearly all cases carcinoma develops. Nevertheless, the removal of the primary ovarian tumor may be followed by disappearance of the peritoneal implants (Pfannenstiel).

It is practically agreed that this type of tumor is derived from germinal epithelium.

Endometrioma.—Sampson maintains that these tumors which he calls "ovarian hematomas (hemorrhagic cysts) of endometrial (Müllerian) type," probably are the most frequent pelvic lesions found at operation in women between thirty years of age and the menopause. Occurring in the ovary they are bilateral in only about one-third of the cases, are usually filled with chocolate colored, viscid or solid material, vary in size from a millimeter to nine centimeters, are either monolocular or multilocular and usually have fairly thick walls. Such masses may occur in the pelvic peritoneum without involvement of the ovary, but more often the peritoneal lesion is secondary to ovarian hematomas. Similar masses may be found in scars of laparotomy, and in the inguinal region. Histologically, they are lined by columnar epithe-

lium and in favorable preparations glands resembling those of uterine mucosa, with characteristic tunica propria, can be identified. These cysts respond in menstruation as does the uterine mucosa, the cyst becomes filled with menstrual blood which subsequently inspissates to form the chocolate mass. In pregnancy they may show decidual reaction (Oberling). Sampson regards the lesion as due to backflow of menstrual blood through the tubes, with lodgment of the epithelium either within a corpus luteum or upon the surface of the ovary. The epithelium is implanted and grows. Rupture of the cyst may discharge similar epithelial masses which lodge upon the peritoneum. Such secondary growths probably constitute the invasive adenomyomas of the pouch of Douglas and the posterial vaginal wall. It is also probable that uterine adenomyoma occurring in the serosal part of the uterus may be of similar nature. Tumors of the same sort are sometimes found on the intestinal surface. Not only are tumors transplanted by rupture of the cyst, but the invasiveness of the tumors and the presence of the discharged blood may be responsible for extensive pelvic adhesions. Sampson's view concerning the origin of these cysts is supported by the experiments of Jacobson, who was able to transplant uterine mucosa in the rabbit with the subsequent formation of cysts similar to those in women, except for the absence of menstrual changes. In spite of this evidence Schickel  explains the condition as due to reversionary proliferation of the pelvic peritoneum, due to chronic inflammation. Others regard it as due to embryonal faults in the M llerian duct.

Carcinoma.—Primary carcinoma of the ovary constitutes, according to the statistics of certain authors, about 10 per cent. of the ovarian tumors. Two groups are recognized, the solid and cystic forms. These tumors occur in the usual age for cancer, but occasional cases are reported in early life. Although the cystic form of primary carcinoma of the ovary may originate as a carcinoma, most of the cases represent a secondary malignant degeneration in cystadenoma, and of the two varieties, the serous papilliferous cystadenoma is the more common point of origin. Not infrequently, the invasiveness of this type of tumor, which distinguishes it from the benign cystadenoma, can be seen with the naked eye. Histologic examination shows the invasive character either in the form of adenomatous groups of epithelial cells or as solid bands of cells traversing the tissues.

The solid primary carcinoma of the ovary is usually unilateral and only rarely exceeds a diameter of eighteen to twenty centimeters. Bilateral involvement is by no means rare, but it is usually difficult to determine whether there are two primary cancers or whether this distribution is due to early metastasis from one ovary to the other. The tumor constitutes a nodular mass which in the earlier stages is encapsulated and covered with smooth, glossy peritoneal surface. Subsequently the tumor breaks through and shows rough, irregular areas in the surface. The consistence varies with the amount of connective tissue, for these tumors may be medullary or scirrhou or intermediate in variety. The cut surface is yellowish-gray or gray, and both its color and consistence depend in part upon the amount of connective tissue present.

Necrosis is fairly common and not infrequently small areas of hemorrhage are observed. Many of these carcinomata are adenomatous in type and may show numerous cystic areas. Histologically, it is usually an adenocarcinoma with considerable irregularity in size and shape of the acini and atypical epithelial cells sometimes in multiple layers. Small solid bands of epithelium invade from the acinar spaces. Carcinoma simplex usually shows more or less interlacing bands of epithelial cells running throughout the tissue. In either

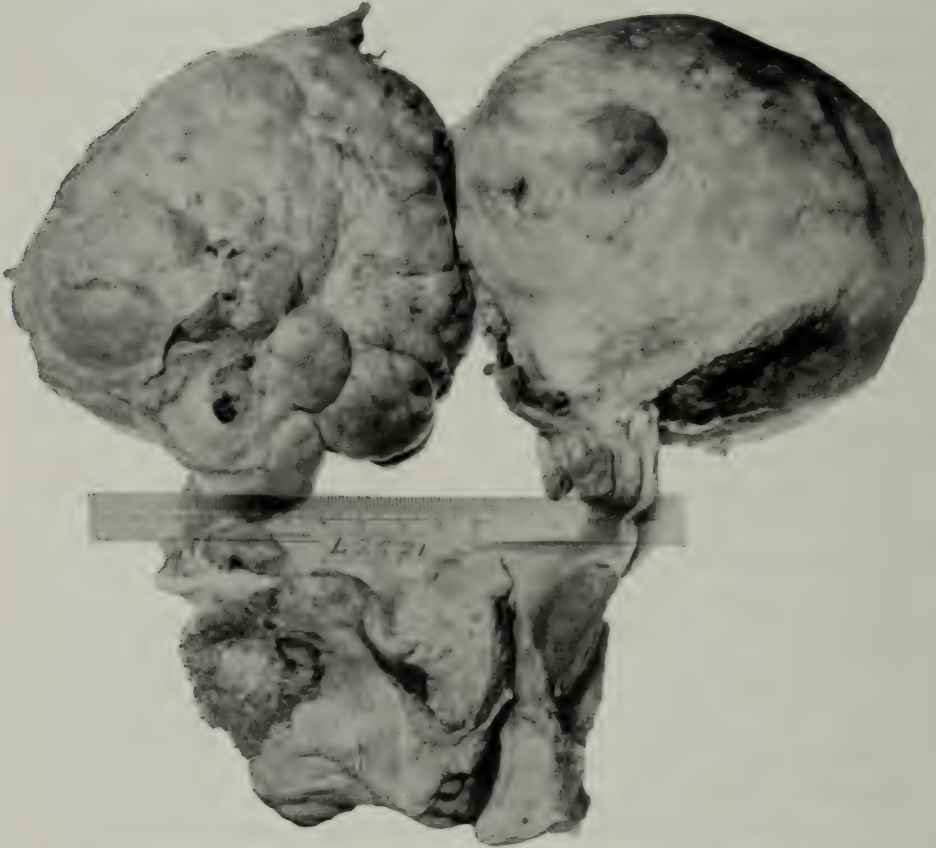


FIG. 361—Bilateral metastatic carcinoma of ovaries secondary to mucoid carcinoma of stomach.

form it is not uncommon to find small calcareous balls, the so-called psammoma bodies. These may be so numerous as to justify the term psammomatous carcinoma. Squamous epithelioma is sometimes observed but this is, in all likelihood, a manifestation of teratoma. Metastasis from primary carcinoma of the ovary is not frequently observed in distant viscera. Metastasis is usually in the lymph nodes of the region and through the lymphatic spaces into the uterus and into the opposite ovary.

Chorionepithelioma is sometimes observed in the ovary but it is more unusual here than in the testis.

Secondary carcinoma of the ovary is frequently bilateral and is usually

derived from tumors of the stomach, intestinal tract or organs of the urogenital system. The exact mode of transfer from the primary site is not clear, but it may be by way of retrograde lymphatic transmission or perhaps also by implantation of small bits of tissue from the primary tumor upon the peritoneum of the ovary. The so-called Krukenberg tumor of the ovary is usually bilateral, with moderate or marked symmetrical and nodular enlargement of the ovaries. Large round globular cells are found, probably of epithelial origin, and in addition the stroma shows proliferation which frequently is of definitely sarcomatous character. The more recent studies of these tumors indicate that practically all of them, with possibly rare exceptions, are secondary cancers of the ovary. The epithelial growth may induce proliferation of the stroma which may ultimately become sarcomatous. The primary tumor is usually in the stomach, but this is not invariably the case.

Sarcoma.—This is an uncommon tumor of the ovary. It is usually unilateral, grows to only moderate size, rarely exceeding a diameter of eighteen to twenty centimeters, may or may not be pedunculated, is usually solid but occasionally shows small cysts. It may be a smooth tumor or distinctly nodular in character, sometimes with glistening outer surface and sometimes with growth of tumor tissue through the capsule. Its consistency varies with the cell character of the tumor. It is usually fairly soft, cuts easily and shows a fleshy, bulging cut surface in which hemorrhage and necrosis are frequent. Histologically, sarcoma of the immature forms is more frequent than the differentiated forms. The latter may be myxosarcoma, chondrosarcoma or angiosarcoma. Giant cell formation may occur in any of the varieties. Telangiectasis of blood or lymphatic vessels is common. Not infrequently the tumor shows a striking perivascular distribution. The spindle cell sarcoma is likely to be the outcome of a preëxisting fibroma or fibromyoma, and in many cases the diagnosis of malignancy is made with difficulty. The round cell tumors may be made up of large round cells or small round cells and not uncommonly show a pseudo-alveolar arrangement. When this occurs with a large round cell tumor the diagnosis of endothelioma is often made. In the ovary, however, it is easily possible that many of these tumors are really epithelial in character. Melanoma of the ovary is usually metastatic from tumors of the choroid or skin, but occasional cases such as those of Winternitz and others are probably primary in the ovary. Sarcoma of the ovary may extend directly to neighboring organs, may be transferred to the regional lymph nodes through the lymphatics, or may be metastatic in remote organs by lymphatic or blood transmission.

Teratoma.—The ovarian teratoma occurs in two forms, the dermoid cyst which is fairly common and the solid teratoma which is rare. The complex dermoid cyst is most frequent in adult life but may occur any time. It is usually a unilateral pedunculated tumor which may vary greatly in size. The outline may be smooth or somewhat nodular and the cyst wall is either thick, or thin with local areas of thickening. In the body it is somewhat fluctuant, but after cooling it is semisolid in consistence. Upon cutting the warm specimen the

cyst is found filled with an oily material, but when cooling occurs this has the consistence of soft soap or may be waxy. This material is probably secreted by sebaceous glands, is fluid at temperatures of 34°C. to 39°C. , and solidifies at temperatures of 20°C. to 25°C. (Wells). It is made up principally of glycerides of fatty acids, cholesterol and other alcohols. Practically always a tangled mass of hair is mixed with the oily material. Most of the hair grows from a knob-like projection from one part of the cyst wall. This presumably represents the anlage of the anterior part of the body and sometimes shows, in addition to the hair, teeth and structures resembling jaw bone. Microscopically, a wide variety of tissues may be identified. The skin shows the hair follicles, sebaceous glands and sweat glands. In addition, the mesoblast may be represented by bone, smooth muscle and a variety of other structures.



FIG. 362—Dermoid cyst of ovary (Gynecological Lab. Univ. of Penna.). From Gynecology, by B. M. Anspach.

Ectoblast may be represented not only by skin but also by various forms of nerve tissue. Entoblast may be represented by various types of glands, intestinal mucosa, stomach and other similar structures. It is of importance that in most of the dermoid cysts the representatives of the three embryonal layers attain a certain amount of maturity, and secondary malignant transformation is not common. Occasionally *epidermoid cysts* are found, without representatives of the other germinal layers.

The solid teratoma of the ovary may be small or may grow to great dimensions. Graves states that less than fifty cases are reported in the literature. They may be smooth or nodular. On cross section they are likely to be spongy because of the presence of numerous small cysts, which may be lined with columnar or squamous epithelium and contain serous, mucous or oily material. Histologically, cell masses of immature or organoid form can be traced to all three layers of the embryo. Malignant change is common and the tumor is then called teratoblastoma. The malignant tissue may be sarcomatous or

carcinomatous. There may be local extension, involvement of regional lymph nodes, or metastasis to remote organs, particularly the lungs. It is probable that struma ovarii which contains true colloid, chorionepithelioma and melanoma, represent one sided development of such tumors. The origin of the various forms of ovarian teratoma has been extensively discussed and is well presented by Graves. There is, however, no decision as to whether they result from development of unfertilized ova or are due to development of primary embryonal germ cells.

Torsion of Pedunculated Tumors.—A moderate degree of twisting of the pedicle is observed in a large number of pedunculated ovarian tumors. This has little significance unless it cause interference with circulation. Torsion through 90° is without effect upon circulation, but through 180° or more is likely to be obstructive. The weight of tumors may lead to sinking into the pelvis, and as this occurs the resistance of the pelvic and abdominal walls as well as intestinal movement may cause the torsion. In general, tumors of the left side show a right spiral and those of the right side a left spiral twist. Ordinarily, the torsion occurs slowly, but in women with relaxed muscles, and in the puerperium, blows, falls or sudden stresses may lead to rapid torsion. Rarely the twist may be reversed upon itself and is then called retorsion. If the tumor be adherent to the gut, torsion may produce intestinal obstruction.

As a rule, the more rapid the rate of torsion the more serious are the results. Interference with venous drainage leads to hyperemia, edema, cellular degenerations and hemorrhage. Occlusion of the arteries causes necrosis and the tumor, especially if cystic, ruptures. If adhesion to the intestine has been established, bacteria may gain access to the tumor and, if there be the changes secondary to torsion, suppuration may occur. Tumors the seat of torsion are probably also more susceptible than otherwise, to the action of bacteria brought by the blood in septicemia and pyemia.

Pregnancy and Ovarian Tumors.—Pregnancy may occur in spite of the presence of ovarian tumors both benign and malignant. Nevertheless the interference with ovulation, as well as the malposition of the uterus which is often associated, probably diminishes the incidence of pregnancy. The increased abdominal pressure of labor may be sufficient to rupture the tumorous and other cysts. Pregnancy favors torsion of pedunculated tumors and this is also particularly true of the puerperium.

Parovarian Cysts.—These are retention cysts in the same sense as those of the ovary. They represent cystic dilatation of the tubules of the parovarium. They therefore originate in the broad ligament near the fimbriated end of the tube and may be either pedunculated or intraligamentary. They are usually only a few millimeters in diameter and multiple, but may be solitary and may attain great size. They are thin walled, monolocular and contain thin, clear, serous fluid of low specific gravity, containing very little protein and no pseudomucin. In the earlier stages the cyst wall and peritoneum are easily separable and the blood vessels of each can be seen coursing in different directions. Subsequently, however, these two membranes may fuse. Usually the

lining is smooth but may show small nodular outgrowths or papillary structures. Microscopically, the cyst wall is made up principally of vascularized connective tissue with small amounts of elastica and smooth muscle. The lining is a single layer of ciliated low columnar, cuboidal or flattened epithelium. The pedunculated cysts may undergo torsion with its consequences as described in ovarian tumors.

Tumors of the parovarium are rare but include fibro-adenoma, papilliferous cystadenoma, teratoma, carcinoma and sarcoma. They should always be carefully distinguished from tumors of accessory or third ovary.

THE BREAST

Congenital Anomalies.—Congenital absence of the breast, amastia, may be unilateral or bilateral, and although more frequent and noticeable in females, occurs also in males. The underlying embryonal fault in the “milk-line” or breast anlage often affects nearby structures, since amastia is frequently associated with anomalies of pectoral muscles, chest and arm. Concomitant anomalies of genital organs and amastia in female pseudohermaphrodites suggest an influence of the sex glands. Athelia or absence of the nipple is rare. It occurs in amastia but may also be observed with a well developed breast. Micromastia and microthelia are usually associated but may be independent of each other and are to be regarded as congenital hypoplasias. Other nipple deformities are flattened nipples and inverted nipples.

Polymastia, or excessive number of breasts, is not infrequent. The milk-line of the embryo extends from the axilla to the inguinal region and the supernumerary breasts may occur at any corresponding situation. With extreme rarity they may appear upon the thigh. They are most frequent in females and in the axilla. They usually enlarge in periods of lactation and may secrete milk. If there be no nipple the swelling of lactation is often painful and may lead to inflammation. It is probable that supernumerary breasts are more susceptible to malignant tumors than normal breasts. Polythelia, or supernumerary nipples, is rare. The extra nipples may be in the areola or on other parts of the breast. When extra nipples occur elsewhere than on the normally situated breast they have underlying breast tissue and are a part of polymastia.

Acquired Anomalies.—Abnormal enlargement of the breast in females is called hypertrophy and in males gynecomastia. Hypertrophy of the breast is usually bilateral but in occasional cases only one breast is affected. Although hypertrophy may rarely be congenital or occur in early life, it usually arises at the period of puberty and less commonly in pregnancy or lactation. The enlargement is usually uniform and may reach enormous proportions. Microscopically, the breasts show increase in amount of gland tissue and supporting tissue, but in some cases there may be dilatation of ducts or even adenoma-like hyperplasia of glands. The cause is unknown. Family incidence is unusual; morphologic disease of sex glands is not common; and hormonal influence, although perhaps of importance, is difficult to apply in cases of unilateral hypertrophy. Diffuse lipomatosis of the breast or large nodular lipoma should

not be confused with hypertrophy. Destruction of breast tissue may be followed by a compensatory hypertrophy of the remainder of the gland.

Gynecomastia signifies the occurrence in the male of breasts simulating those of the female. A rare condition, it is usually bilateral but may be unilateral. Familial incidence strongly suggests hereditary influences. It may be a reversionary phenomenon. It constitutes a part of the feminine habitus in diseases of the organs of internal secretion. It may develop following disease, atrophy, or removal of testes. Grossly and microscopically, it resembles the female virgin breast.

Atrophy, except that of age, is uncommon. Rarely postlactation involution may progress to atrophy. Local atrophy may occur as the result of pressure from tumors.

Circulatory Disturbances.—The breast may be somewhat enlarged and hyperemic in the premenstrual phase, and from the nipples a few drops of blood may be discharged. Bleeding from the nipples may be due to both benign tumors, especially the papilliferous adenoma, and to malignant tumors. Small or large hemorrhage into the breast may be due to trauma or may be without known cause. The larger hemorrhages have been given the name apoplexy of the breast (see Cutler).

Inflammation.—Non-suppurative diffuse inflammations are seen in the newborn. In the adult they are due to retained secretion dammed back by fibrous occlusion of ducts, inspissation of secretion in the nipple ducts, or by athelia. The suppurative inflammations usually occur during lactation, presumably because of infection travelling up the ducts. With or without retention of secretion, suppuration begins in the ducts or glands and involves the supporting tissues. Sometimes the inflammation is found only in and under the nipple; it forms a subareolar abscess. Originating in breast infection, the abscess may be intramammary, subcutaneous or, when it occurs beneath the breast and on the chest wall, submammary. The more extensive forms may become phlegmonous. Abscesses of the breast may occur in pyemia or may extend from suppuration in the chest wall or thorax. It is conceivable that in septicemia the excretion of bacteria in the milk may excite inflammation and suppuration. This is a possible explanation of the acute mastitis which sometimes complicates typhoid fever. In mumps there may be a so-called metastatic acute mastitis. Trauma may cause acute mastitis and in the male is the commonest causative factor. Acute suppurative mastitis is usually due to staphylococcus aureus, but other pyogens may also be causative.

The abscess may result in complete cicatrization following evacuation, or the granulation tissue may become dense and form a chronic abscess. Occasionally, the contents are completely liquefied, become serous in character by removal of solid particles, and the wall condenses to form a pseudocyst. The chronic abscesses may be mistaken clinically for tumor. Microscopically, it is not uncommon to find in the abscess pseudotubercles with foreign body giant cells surrounding small particles of tissue detritus or cholesterol crystals.

Chronic mastitis may follow the acute forms or be a chronic fibrosing process from the start. The chronic hyperplastic mastitis, seen especially in the male breast, is often without history of preceding acute inflammation. It is a progressive connective tissue hyperplasia which may produce moderate enlargement of the breast. In the female, chronic mastitis usually follows some form of acute mastitis. In the majority of cases it is merely a cicatrization of the old process and not progressive. In other cases, however, the firm area may enlarge somewhat and show microscopically a sufficient infiltration of lymphoid and plasma cells, together with epithelial proliferation, to justify the assumption that it is a chronic inflammation. The so-called chronic cystic mastitis will be discussed under the heading of cysts of the breast.

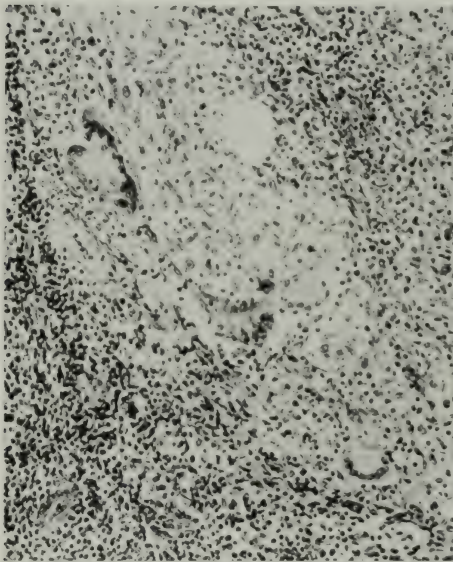


FIG. 363—An area in chronic abscess of the breast with multinucleated giant cells.

Infectious Granulomata.—Tuberculosis may affect the skin of the breast in the form of lupus. In rare cases, tubercle bacilli may enter the breast through abrasions of nipple and skin. Tuberculous mastitis, however, is usually secondary to tuberculosis elsewhere, especially of the lungs and of the lymph nodes. Deaver and McFarland accept as authentic the reports of ninety cases, of which only ten were in the male breast. It does not occur before puberty, may be seen in advanced years, but is most frequent in the third and fourth decades of life. Anspach found that 70 per cent. of his cases were in married women but less than half of these were parous. Since the early stage is usually found in ducts or glands, it seems probable

that the lesion is due to excretion of tubercle bacilli into the lumen and subsequent tubercle formation. It is also probable that infection may occur from retrograde lymph transport from lymph nodes or mediastinum or axilla, but it is difficult in such cases to decide that the lymph node involvement is not secondary to the breast lesion. According to Deaver and McFarland the tuberculosis may be (1) miliary, (2) conglomerate with large single or multiple nodular masses, (3) sclerosing tuberculous mastitis, comparable to chronic fibroid tuberculosis of the lungs, (4) mastitis tuberculosa obliterans in which chronic periacinar and periductal tuberculosis leads to obliteration of the breast epithelium, and (5), various atypical forms. In the more extensive lesions, sinuses not infrequently discharge through the skin. Tuberculosis may be associated with benign or malignant tumors (Warthin) or with other lesions of the breast, but should always be distinguished from pseudotubercles as mentioned in reference to chronic abscess. The diagnosis depends not only upon

the presence of histologically demonstrable tubercles, but must be supported by bacteriological evidence.

Syphilis may affect the breast as chancre, as mucous patches or other secondary cutaneous lesions, as gumma, and as a diffuse chronic inflammation with diffuse and perivascular lymphoid cell infiltration associated with endovascularitis (Wood). Actinomycosis and sporotrichosis may be primary in the breast.

Cysts.—Cysts of the breast may be the result of a wide variety of conditions including retention of secretion, accumulation of serous fluid, inflammation, hyperplasia, abnormal involution, tumor growth. In addition there are pseudocysts resulting from encapsulation of abscess or hemorrhage.

Galactocele is a retention cyst of the ducts, usually single but sometimes multiple, whose origin is often without explanation. The content may be milky, may be like butter or may be thin and serous, with or without casein flakes.

Simple cysts usually appear as fairly large single cysts, often with associated cystic dilatation of neighboring ducts, with chronic inflammation or with abnormal involution. The wall is thin and when approached surgically in the living breast has a blue color, the blue dome cyst of Bloodgood. As soon as the cyst is cut the blue color disappears. The fluid is thin, serous, clear or turbid, sometimes viscid but never milky. The lining is smooth. The papilliferous cyst is of the same general sort but does not have the blue dome, shows papillary outgrowths of lining epithelium and contains usually blood tinged fluid. It may be associated with the same conditions as is simple cyst. Many cases are benign but malignant change is common. Bloodgood designates as "cancer cysts" those with smooth walls, without papilloma but containing bloody fluid or thick, grumous material. He found cancer or sarcoma in the walls of such cysts.

Abnormal Involution of the Breast.—This is considered with cysts because one of the outstanding features is the formation of multiple small cysts. The condition is sometimes unilateral but is usually bilateral and occurs most frequently in women who have at some time lactated, although it may occur in virgins. It is a disease of mature life, especially at about the time of menopause. Early symptoms include pain, discharge of blood or secretion from the nipple and the palpation of one or several small nodules or "cords" in the breast. Grossly, the breast is usually not enlarged and the condition is not circumscribed or encapsulated. The organ is dense and firm and in cross section shows usually a variable number of small cysts, or even a single "blue dome" cyst. Microscopically, the connective tissue is densely fibrillar but not notably increased in amount and may show a rich infiltration of lymphoid cells. The cysts are found to be dilated ducts, but microscopically the glands also may show irregular cystic dilatation, apparently an adenomatous hyperplasia. Some of the acini show papilla-like spurs which are probably due to fusion of adjacent acini and rupture of their walls. The epithelium may be piled up in several layers. The epithelium of many acini shows a markedly eosinophilic cytoplasm. Other acini show cells resembling those of sweat glands, which led Krompecher to regard the condition as a hydrocystoma

mammæ. The basement membrane is nearly always intact but pictures suggesting penetration are observed. In the opinion of most observers the lesion may become cancer but the chance of this has probably been much overestimated.

Opinion as to the nature of the condition varies widely. McFarland has found all the microscopic changes indicated above in postlactation involution of the breast, and with Warren, regards the condition as an abnormal involution. Bloodgood and many others regard it as inflammatory and call it chronic cystic mastitis, a term widely accepted. McFarland points out that the chief indication of chronic inflammation, the lymphoid cell infiltration, occurs in normal involution. Schimmelbusch called the condition cystadenoma, but it is not a tumor. Reclus named it cystic disease of the breast, a term of vague meaning. In fact, Deaver and McFarland list twenty names that have been given to this or closely related conditions. This is sufficient to indicate the differences of opinion concerning the nature of the condition. Even with acceptance of McFarland's view it is of importance that other modern students,

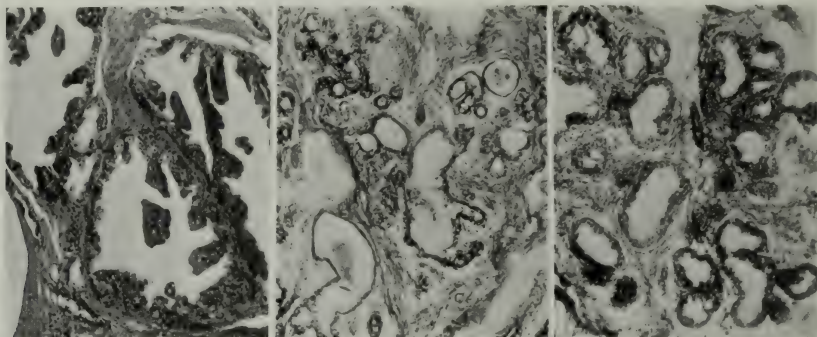


FIG. 364.—Three photomicrographs from abnormal involution of the breast to show various types of epithelial change and cyst formation.

including Ewing, regard the lesion as inflammatory. Nevertheless, there may be associated inflammation or tumor growth.

Tumors.—Benign tumors of the breast include foremost the fibro-adenoma. Fibroma and myxoma occur but are rare. Lipoma is not uncommon and may be bilateral. Osteoma and chondroma and osteochondroma may occur as the result of differentiation of the connective tissue of a fibroadenoma, or they may occur as primary tumors, perhaps of embryonal origin, and therefore to be regarded as teratoid in nature. The adenoma will be referred to after the discussion of fibro-adenoma.

Fibro-adenoma is essentially a mixed tumor consisting of connective tissue and epithelial elements. According to McFarland, these tumors constitute about one-fourth of the tumors of the female breast. They are distinctly unusual in the male breast. Although they may occur in early life and in late life, the average age is thirty-two years. Of these women, 75 per cent. have not borne children and 95 per cent. have not reached the menopause. Although usually single, the tumors may be multiple. They are slow growing, dense, usually painless masses, which ordinarily are brought to the attention of the

surgeon when they have attained a diameter of about three to six centimeters. The tumor is firm, dense, smooth in outline or slightly nodulated, well defined and shells out easily from the surrounding tissue. It usually cuts with considerable resistance and shows a gray or grayish-pink, firm, fibrillated cut surface, although it may be soft, or gelatinous in character. Sometimes the cut surface shows clefts or small cysts but is practically never lobated. Microscopically, proliferation of connective tissue and of epithelium are found. It is possible to distinguish three general types although often enough these are intermingled. The intercanalicular variety shows diffuse connective tissue proliferation with a relatively small number of tubular epithelial spaces. In the pericanalicular variety the connective tissue shows dense and often concentrically arranged connective tissue masses immediately around the epithelial



FIG. 365—Intracanalicular fibroadenoma of the breast.

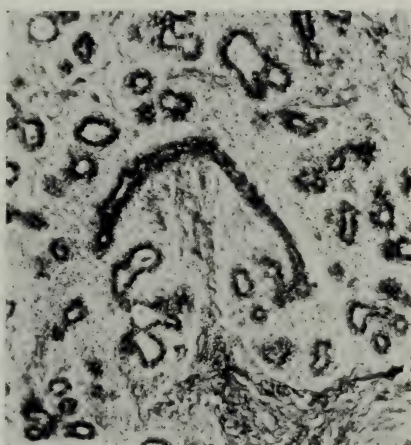


FIG. 366—Adenoma of the breast with edema of supporting tissue.

areas. In the intracanalicular fibro-adenoma there is a considerable proliferation of epithelium arranged in more or less stellate figures. This peculiar configuration is presumably due to ingrowth into the canal of blunt projections or papillæ of connective tissue. The lumina of the epithelial spaces are likely to be obliterated, and the epithelium is disposed in parallel rows of cells. In all the varieties of fibro-adenoma the epithelial spaces usually are lined with only a single layer of cuboidal epithelium, resembling that of the finer ducts. Occasionally, the epithelium is in double layers resembling more closely that of the glandular acini. As a rule, the connective tissue is moderately cellular but may be of densely fibrillar character. Edema is not infrequent especially in those parts of the connective tissue immediately around the epithelial acini. Muroid degeneration is also common and occasionally fat infiltration is observed.

Closely related to the fibro-adenoma is the so-called cystosarcomaphyllodes. This is a more or less cystic tumor with connective tissue papillary growth into

the cystic areas. It was formerly thought that these connective tissue papillæ are of sarcomatous nature, but modern investigation indicates that they are probably not malignant.

Adenoma of the breast is a distinctly uncommon tumor. Grossly, except in density of consistence, it resembles the fibro-adenoma, but microscopically it shows extensive multiplication of glandular acini which may be uniform, regular and small, or may be very irregular in outline and with multiple layers of cells. This is referred to as the solid adenoma in contrast to the cystadenoma. Usually, however, the cystadenoma is classified as a fibro-adenoma with cystic dilatation of the epithelial spaces. It is probable that many of the cysts discussed in the preceding section are of this character.

Carcinoma.—According to MacFarland, carcinoma of the breast constitutes about three-fourths of the breast tumors. It may occur in early life or

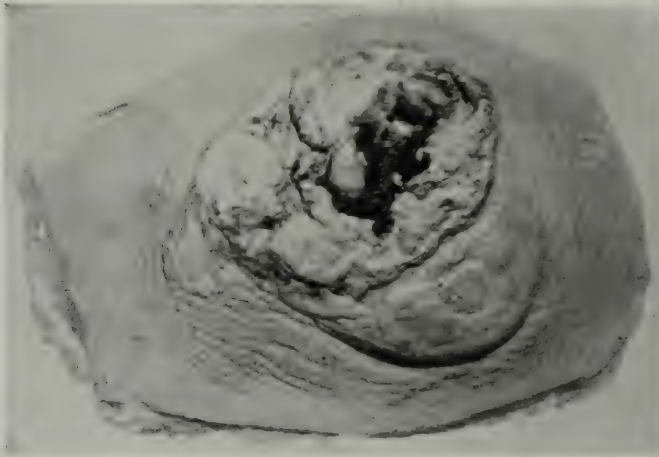


FIG. 367—Medullary carcinoma of breast with penetration of skin.

in late life but is especially frequent between forty and sixty years of age, occurring in the upper outer quadrant of the breast in about half the cases. It is at least one hundred times more common in the female than in the male breast. It is usually first observed as a lump in the breast which may grow rapidly or slowly, is firm, poorly defined and adherent to the surrounding breast tissue. The commoner forms include the soft, medullary, or encephaloid cancer and the firm, scirrhus cancer. Either form may grow up to and into the skin and penetrate through it to produce a small or large ulcerated area, but this is more especially true of the medullary cancer. Contraction of connective tissue may produce depression or actual inversion of the nipple, more especially in the scirrhus cancers. Sometimes the retraction is seen particularly in the connective tissue columns of the skin, producing the so-called pigskin, or the skin may be flat and glossy. Rarely, the tumor may extend laterally underneath and through the skin to form the *cancer en cuirasse*. Microscopically, the tumor may appear as a carcinoma simplex or an

adenocarcinoma. Most of the true cases of cancer leave no reasonable doubt as to the diagnosis. The greatest difficulty is encountered in diagnosing malignant change in abnormal involution of the breast or in fibro-adenoma of the breast. In the scirrhus carcinoma, carcinoma simplex is more common than adenocarcinoma although the latter is sometimes observed. Less common varieties of the carcinoma of the breast include the psammocarcinoma and the mucinous carcinoma. Rarely, the epithelium constituting the carcinoma may undergo metaplasia with the formation of stratified squamous epithelium. This should not be signified as a squamous epithelioma. When true squamous epithelioma is observed in the breast, it is the result of extension from the skin.

On the basis of the histology of mammary cancers, Greenough finds that the prognosis can be determined with a fair degree of assurance by observing the degree of differentiation of the constituent epithelial cells. Those of low differentiation as to cell morphology, size and arrangement are almost invariably fatal. "A tumor of adenomatous arrangement (adenocarcinoma),

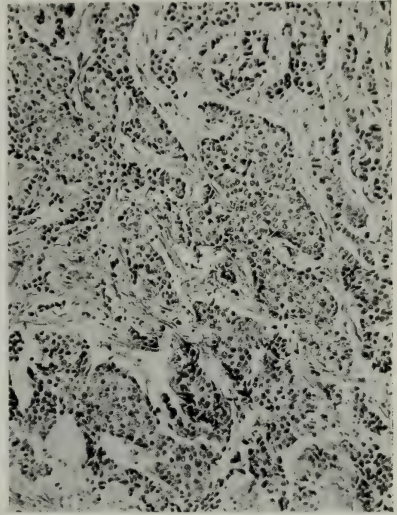


FIG. 368—Medullary carcinoma of breast (carcinoma simplex).

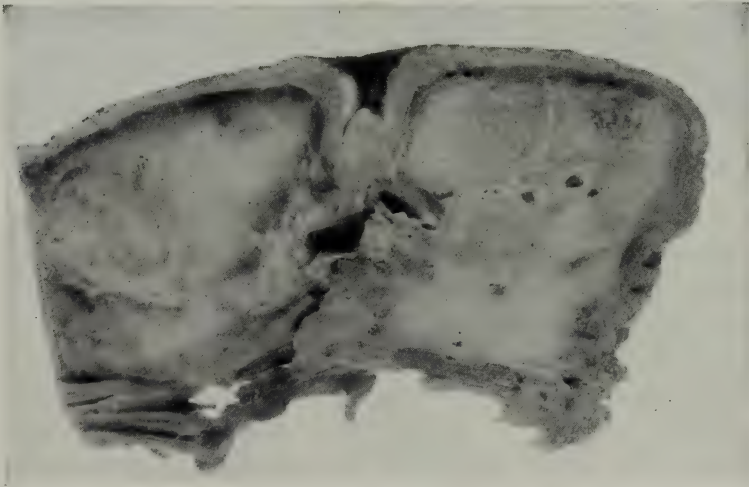


FIG. 369—Cross section of breast with scirrhus carcinoma, small cysts, and marked retraction of nipple.

with uniform sized cells and nuclei, few mitoses, and absence of hyperchromatism, indicates low malignancy." An intermediate grade can be distinguished. He finds that lymphoid infiltration and hyalinization of connective tissue are not indicative of resistance.

The metastasis of carcinoma of the breast has been studied extensively by Handley. His theories concerning this matter have been discussed in the chapter on general pathology of tumors. Metastasis is most frequently observed in the lymph nodes of the axilla, but in microscopic diagnosis care should always be exercised to differentiate between tumor metastasis and endothelial hyperplasia which is extremely common. The hyperplasia of the lymph nodes is regarded by some as preparing the soil for metastasis. This hypothesis, however, is not certainly established. Many cases of cancer of both breasts represent metastasis from one breast to the other, but occasionally cancers may develop simultaneously in the two organs. The pectoral muscles, the lymph nodes of the thorax and the lymphatic tracts and lymph nodes of the abdominal cavity may be involved by lymphatic metastasis. Remarkable

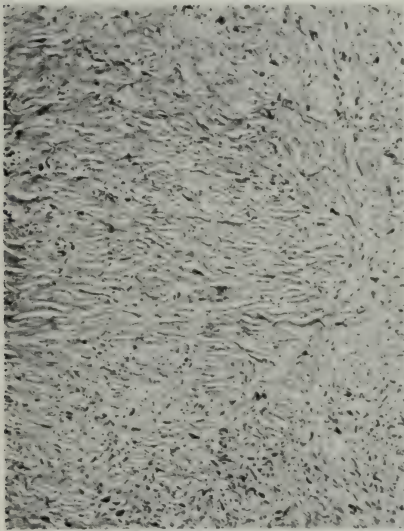


FIG. 370—Scirrhous carcinoma of breast.

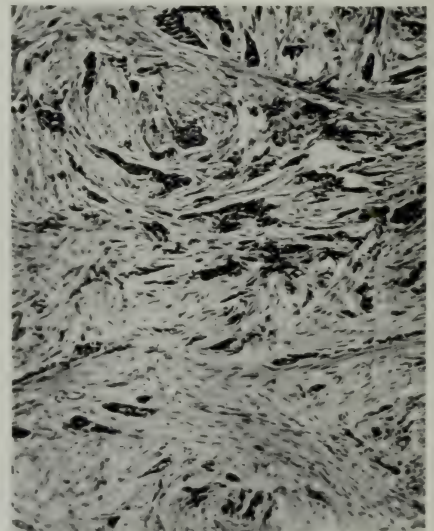


FIG. 371—Fibrous carcinoma simplex of breast.

distant lymphatic metastases are sometimes observed far removed from the original site, for example in the thigh or leg. Rarely, the lesion may invade blood vessels and produce blood borne metastases or generalized carcinomatosis.

Sarcoma of the breast is relatively infrequent but occurs far more often in the female than in the male breast. It may be seen at any period of life but is most frequent between thirty and fifty years of age. Those that develop in the periductal tissue are said to be indigenous, and those that develop in the outlying supporting tissues are said to be non-indigenous sarcomas. Sarcoma often grows and develops as does the adenofibroma, may be removed with this diagnosis and is found only upon microscopic examination to be malignant. Some sarcomas show a sudden increase in rate of growth, whereas others appear to grow rapidly from the beginning. When the tumor has attained considerable size, the superficial veins of the breast are distended. Erosion of the skin is common. Microscopically, the most frequent sarcoma is made up

of spindle cells. Round cell sarcomas occur but must be carefully differentiated from epithelial tumors. It is probable that many of the more highly differentiated sarcomas such as giant cell sarcoma, osteo- and chondrosarcoma, etc., represent malignant change of teratoid tumors. Sarcoma may be combined with carcinoma.

Paget's disease of the nipple begins as a dermatitis on the nipple and areola, principally in women forty to sixty years of age, and may extend slowly to the surrounding skin. In early cases there is a subacute or chronic inflammation of the corium with moderate dipping of the epithelium between the papillæ. The epidermis thickens and the deeper transitional and sometimes the basal cells show much increase in size, because of swelling and vacuolization of the cytoplasm. Subsequently, epithelial proliferation becomes marked, epidermoid carcinoma may develop and may extend deeply into the breast (see Bloodgood).

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CHAPTER XX

THE DUCTLESS GLANDS

HYPOPHYSIS.
PINEAL GLAND.
THYROID GLAND.
PARATHYROID GLANDS.
THYMUS.
ADRENALS.

Introduction.—In this chapter the discussion will be limited to the hypophysis, the pineal, thyroid and parathyroid glands, the thymus and the adrenal bodies. This by no means exhausts the organs which provide internal secretions. The pancreas, testis and ovary have been considered in other chapters. Other organs suspected of providing internal secretions have also been discussed, but that liver, kidney, lymph nodes, spleen, etc., elaborate hormones, is by no means proven. All organs and cells excrete or secrete substances into the body fluids, many furnish products which are utilized for metabolic activity, but only a few are proven to secrete hormones, chemical substances secreted into the body fluids, circulating therein, influencing growth, metabolic and other activities and interchangeable between species. There is undoubtedly influence of one endocrine organ upon another and it is likely that the activities of the whole group are interrelated. Such organs suffer afunction when the hormonal activity is absent, hypofunction when there is a decreased activity due either to diminished output of secretion or suppression through the antagonism of other hormones, and hyperfunction when there is excessive secretion or decrease of antagonistic hormones. The term dysfunction implies a qualitative alteration of the secretion whereby the activity of the hormone is altered, but a proven example of this condition cannot be offered. Certain authorities, however, use the term dysfunction to cover stages in which it is difficult or impossible to determine whether there is hypo- or hyperfunction. Each section of this chapter will present the morphological alterations, to be followed by a brief discussion of the functional disturbances.

THE HYPOPHYSIS

Congenital Anomalies.—The hypophysis is formed by the junction of an entodermal pouch from the roof of the buccopharyngeal junction, which ultimately constitutes the pituitary gland, and a bud from the anterior cerebral vesicle which constitutes the infundibular process. This division of the adult hypophysis into pituitary gland and infundibular process accords with that of Tilney and Riley. A remnant is practically constant under the pharyngeal mucosa, the pharyngeal hypophysis or *Rachendachhypophyse*. Accessory hypophyses may be found in the pharynx, the sphenoid bone and the sella turcica. Dandy and Goetsch describe in the dog and cat a parahypophysis

made up of chromophobe cells in the floor of the sella. Congenital hypoplasia of the pituitary gland is common in cretins and other types of dwarf.

Retrogressive Changes.—Atrophy usually affects principally the pituitary gland and shows decrease in chromophile cells with fibrosis. It occurs in old age, as the result of pressure, and sometimes is seen in myxedema, exophthalmic goiter, arteriosclerosis, alcoholism, diabetes mellitus (Kraus) and other diseases.

Pigmentations, calcification, cloudy swelling, amyloid and necrosis are occasionally observed. The "colloid" of the pars tuberalis or intermedia may be much increased. In infectious diseases, so-called toxic necroses are sometimes observed, but that these are of toxic nature is not supported by the

experiments of Weithold. Circulatory disturbances include passive hyperemia, dilatation of veins, various forms of arterial disease, embolism and infarction.

Inflammations.—Inflammations of meninges and of neighboring bone may extend to the hypophysis. Metastatic abscesses and infarcts may occur in septic diseases but are unusual in such diseases as scarlatina, diphtheria, measles, typhoid, etc. (Plaut). Tuberculosis may affect the hypophysis by direct extension or by blood transport. Syphilis, both acquired and congenital, may be present as diffuse mononuclear cell infiltration, foci of necrosis, gumma formation, or fibrosis (Jaffe, Nonne, Schmitt).

Progressive Tissue Changes.—

Hyperplasias affect the pituitary

gland rather than the neural infundibular process. The cells concerned are usually the chromophobe or chief cells, which normally are situated in the middle of the cell columns. Acidophile cells may be solely involved in the hyperplasia. Hyperplasias of pregnancy (see Erdheim) are to be regarded as part of a normal cycle in the gland, but may readily be confused with and perhaps change into pathological states. The distinction between hyperplasia and diffuse adenomatous struma is difficult in many cases. Even focal adenomas may apparently occur and disappear in the course of hyperplasia.

Tumors.—Tumors may arise from various parts of the hypophysis, (1) the pars distalis or the pituitary gland and the pars tuberalis (pars intermedia), (2) the pouch of Rathke and its derivatives, (3) the infundibular process (pars nervosa).

The adenomas of the pituitary gland, if diffuse, are difficult to distinguish

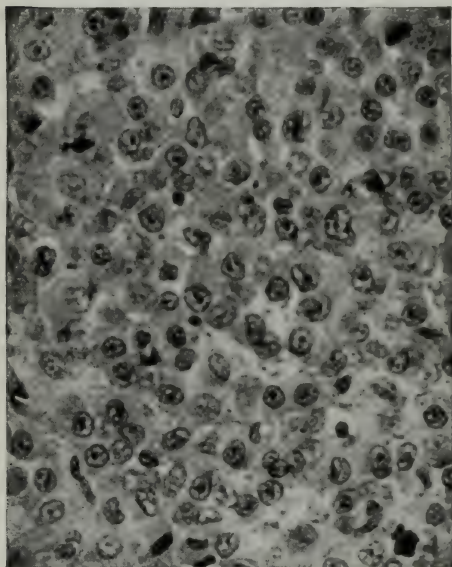


FIG. 372—Chromophobe struma of pituitary gland. From Cushing, H., *The Pituitary Body and Its Disorders*.

on the one hand from hyperplasias and on the other from carcinoma. The focal adenoma may be single or multiple, The gland therefore may be diffusely enlarged or nodular. The cellular arrangement may follow fairly closely the architecture of the gland or may be strikingly atypical. Chromophobic cell adenomas are apparently most common (see Bailey), but eosinophilic cell and basophilic cell adenomas may occur. The most careful technique is necessary in order to distinguish the cell types (Bailey, Lewis).

The adenocarcinoma is, according to Ewing, a frequent tumor of the pituitary and is characterized by local invasiveness. The cell picture varies as with the adenoma. It is often difficult to judge whether destruction of the sella and other surrounding areas is due to pressure of benign tumors or invasion by malignant tumors, and this increases the difficulty in determining the character of the tumors. Sarcomas are reported but it is likely that most of these are atypical carcinomas or adenomas. Any of the epithelial tumors

may become cystic by necrosis or by the production of colloid or other secretion.

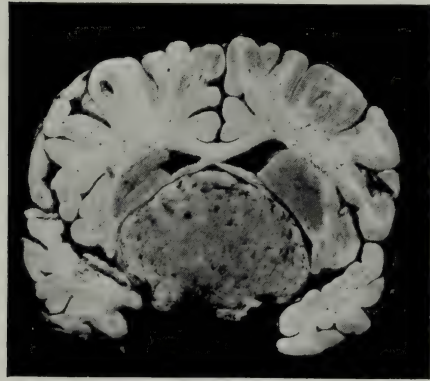


FIG. 373—Meningioma of hypophyseal region.

Tumors of the duct of Rathke, or its derivatives, may occur anywhere along its course, but are most common in the hypophysis. They are usually cystic and may be lined by cuboidal or intermediate stratified epithelium or by squamous epithelium. Gland spaces and small cystic dilatations may occur. Fluid secretions, colloid, cholesterol crystals, calcium deposits and bone formation are not infrequently observed.

More or less complicated mixed tumors derived from ectoblast, mesoblast or entoblast, are presumably due to embryonal displacement and may contain various types of epithelium, neuroglia, bone, muscle, etc.

Glioma, lipoma and tumors probably derived from the cells of the pituitary, are reported in the infundibular process.

Physiological Considerations.—The experiments of Cushing and of Simmonds indicate that complete removal of the hypophysis results in death, but Sachs and Macdonald maintain that if the hypothalamus be uninjured in the operation, excision of the hypophysis is not fatal. Removal of the infundibular process is certainly not fatal (Cushing). Cushing has shown that experimental hypopituitarism in puppies leads to inhibition of skeletal growth and of sexual development, psychic disorders and apiposity, which corresponds closely to Fröhlich's syndrome or dystrophia adiposogenitalis. In adult animals there develops "adiposity, increased sugar tolerance, lowered body temperature, and reversible sexual changes." Such conditions in man may be due to destruction of the pituitary gland by destructive inflammatory lesions, tumors of the pituitary, pressure from tumors of the duct of Rathke and

neighboring parts of bone and brain. An additional symptom of dystrophia adiposogenitalis, sexual infantilism, often with atrophy of the sex glands, is observed in such cases and occurs in experimental animals. It is possible that interference with the discharge of secretion of the gland may give rise to the same syndrome, but in view of the fact that the mode of entry of the secretion into the body is as yet unknown (Bailey), this point is difficult to prove.

Akromegaly, with its enlargement of the skeleton, mandibular prognathism, thick skin, large hands and feet, heteronymous hemianopsia and other visual defects (deSchweinitz) polyuria and glycosuria, is apparently due to oversecretion and enlargement of the hypophysis. In many such cases adenoma or adenocarcinoma or merely hyperplasia of the pituitary are found. Such conditions exist, however, without akromegaly, and cases of akromegaly occur

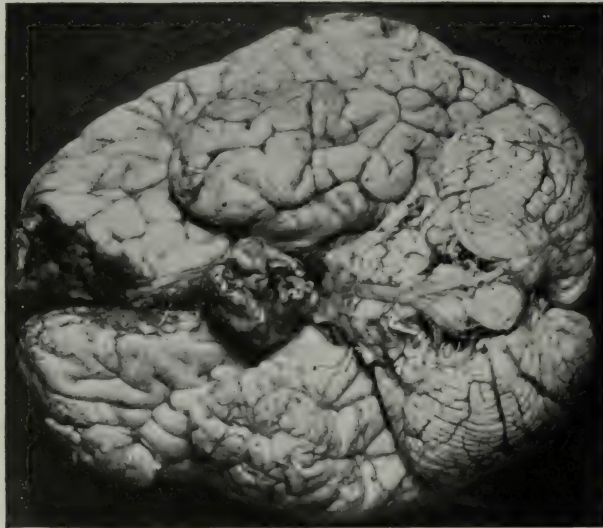


FIG. 374—Cyst of hypophyseal region.

without tumors of the pituitary gland. It is easily possible that diffuse adenomatous hyperplasias or focal adenoma may exist long enough to produce akromegaly, and then regress so that at the time of autopsy there is no important lesion. The studies of Bailey and Davidoff indicate that the lesion is usually, if not always, an adenoma of the pituitary gland composed of chromophile cells with alpha (acidophilic) granules. Akromegaly is a disease of adult life. It is supposed that the same excitation in earlier life leads to gigantism (Biedl). Although experiments with mammals have not been conclusive, such work as that of Uhlenhuth with salamanders indicates that the anterior lobe has a definite growth promoting power (see also Evans). Robertson's tethelin may well represent the active principle of this secretion. Pituitrin is the name given the polyuria producing, pressor, smooth muscle stimulating active principle of the infundibular process (Abel); and the polyuria and reduced sugar tolerance of akromegaly may be due to some

disturbance in the secretion of this principle, but there is no outspoken morphologic evidence of this in the organ. Diabetes insipidus with its polyuria and thirst, but without functional disease of the kidney, is thought by some to be due to deficient activity of the infundibular process. Sometimes definite lesions of the hypophysis are found (Piney and Coates). The symptoms are often relieved by administration of pituitrin (see Christie and Stewart). Tierney

however, expresses the view that a true hormone of the infundibular process has not yet been demonstrated. The work of Bailey and Bremer and of Curtis has shown that a polyuria in animals similar to diabetes insipidus in man, may be pro-

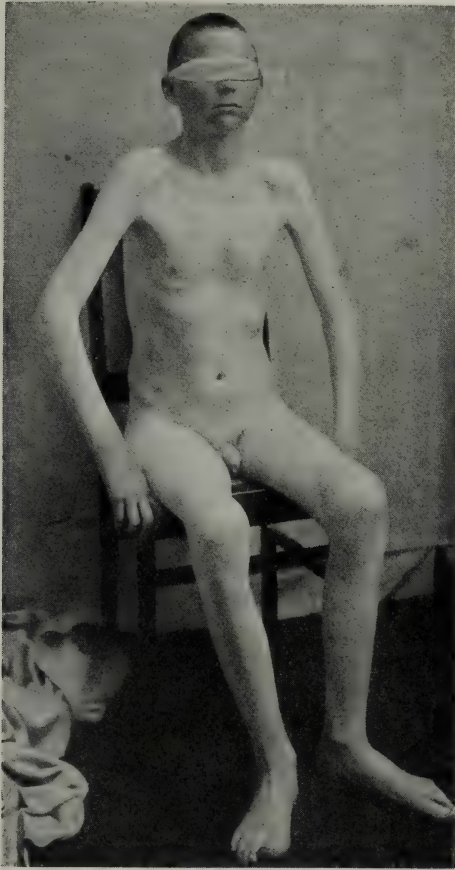


FIG. 375—A boy eighteen years of age, with destruction of sella turcica, genital aplasia and absence of hair on pubes, face and in axillæ, the victim of hypopituitarism. Referred to E. C. Cutler, M. D.

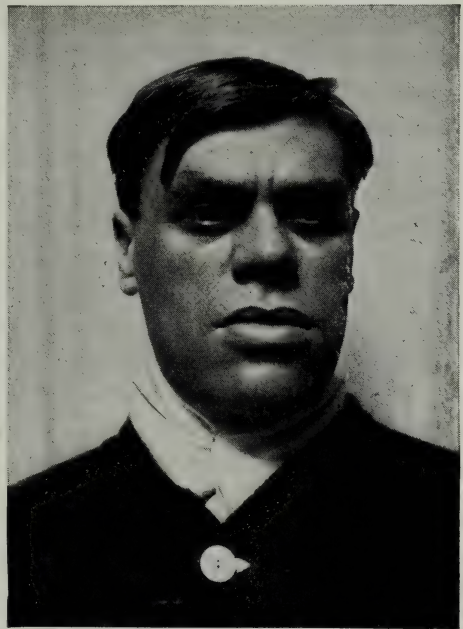


FIG. 376—Outspoken akromegaly from adult hyperpituitarism. From Cushing, H., *The Pituitary Body and Its Disorders*.

duced by injury to the hypothalamic region without lesion of the hypophysis.

There are no fixed and constant lesions of the hypophysis associated with the two more or less characteristic syndromes mentioned in connection with deficiency or increase of hypophyseal activity, and many confusing clinical manifestations occur. Of great importance are also the "neighboring" phenomena such as those due to increased intracranial pressure and the optic disturbances of the hypophyseal tumors.

The relationship to other ductless glands is close but requires much further study. Thus, the hyperplasia of pregnancy probably has to do with a secretion

from corpus luteum. Gonad atrophies and, according to Cushing, pancreas lesions have an influence upon the hypophysis. Conversely, lesions or destruction of the hypophysis may result in thyroid hyperplasias, persistence of thymus, hypertrophy of adrenal medulla, hypoplasia of the gonads, fatty changes and even necrosis of the liver. Evans holds that "the anterior hypophysis is indispensable for growth to adult stature" and that the "hypophysis stands in a necessary relationship to normal function of thyroid, sex glands and adrenal cortical tissue."

THE PINEAL GLAND

General Pathology.—In the course of involution of the gland, multiple small cysts of the acini may occur. Much more common are fairly diffuse or focalized, microscopically laminated, sand-like deposits of phosphates and carbonates of lime, which may give a shadow in x-ray plates. In infectious diseases small hemorrhages may occur and in meningitis the gland may be the seat of suppuration. Tubercles and gummata are rare; the gland may show a diffuse round cell infiltration in congenital syphilis. Hyperplasia may occur (Bell).

Tumors.—Tumors of the pineal are infrequent. Although glioma, angiomatous and fibromatous tumors are said to occur, the principal tumors are, according to Horrax and Bailey, the pinealoma made up principally of cells resembling adult pineal parenchyma cells, pineoblastoma made up of primitive cells of the same order, and teratoma probably derived from residual blastomere cells. Tumors may grow out over the tentorium cerebelli or into the third ventricle. They may compress such neighboring structures as the crura cerebri and basal ganglia, and by compression of the aqueduct of Sylvius produce internal hydrocephalus. The pressure of fluid may distend the recessus of the infundibular process with marked compression of the hypophysis in the sella.

Physiological Considerations.—The pineal is apparently not essential to life. Immediate effects of extracts have not been clearly demonstrated. McCord, however, claims that prolonged administration of extracts to young animals increases rate of growth and produces early sexual maturity. Whereas Dandy's experiments with total extirpation of the pineal failed to induce noteworthy change in growth, sexual development or metabolism, the experiments of Horrax, Izawa and others, show excessive growth of gonads and early development of secondary sex characters. Thus, as Hewlett points out, administration of extracts and extirpation of the gland apparently produce much the same changes. Clinically, lesions of the pineal, more especially tumors, may produce definite signs and symptoms. Tumors developing before puberty may produce signs of brain tumor only or may lead, practically solely in males, to precocious sexual and mental development, early development of secondary sex characters and increased body growth (Horrax, Izawa). Adiposity which is often the only extracranial sign in adult patients, is probably due to alteration of metabolism (Marburg). Whether cachexia, which some-

times occurs, is due to hydrocephalus or the pineal involvement is not yet clearly determined (Bailey and Jelliffe). Krabbe maintains that no convincing evidence of an internal secretion of the pineal has been adduced. In both experimental and clinical observations it is difficult to determine whether the changes are due to the pineal lesion or to associated change in the hypophysis. There may be involvement of other glands such as atrophy of the hypophysis from pressure, hyperplasia of adrenal cortex and of interstitial cells of the testis, and persistence of the thymus (Sézary).

THE THYROID GLAND

Congenital Anomalies.—The thyroid may be absent. In some such cases a small nodule of thyroid tissue may be found at the lingual end of the thyroglossal duct, and may exhibit the various pathological changes which affect the normally situated gland. Accessory thyroid nodules may be found along the site of the thyroglossal duct or beneath the sternum. Remnants of thyroglossal duct may persist and give rise to cyst formation or to tumor growth. Cell masses of parathyroid and thymus may be included in the thyroid.

Retrogressive Changes.—In a wide variety of infectious diseases, swelling and increased granularity of the epithelial cells, often with vague cell outline, justify the assumption that cloudy swelling occurs. Desquamation and necrosis are common under the same circumstances. The cells normally contain fat and it is therefore difficult or impossible to distinguish fatty degeneration. Hyalin affects the stroma of the gland especially in senile atrophy, long standing goiters and scars. Amyloid of the blood vessels is seen in generalized amyloidosis and occasionally is found limited to the thyroid. Calcification and ossification are common, especially in old goiters, cyst walls, scars and sites of old hemorrhages. The large amounts of colloid in colloid goiters is regarded by some as a sort of colloid degeneration, but is probably only a residuum of cyclic changes in activity and not truly degenerative.

Arteriosclerosis is common in goiters, often quite independent of arteriosclerosis elsewhere. Transitory hyperemia is likely to accompany menstruation and pregnancy. Prolonged hyperemia is seen in hyperplasias and various forms of goiter and may produce tortuosity of the vessels. Passive hyperemia may accompany the general passive hyperemia of heart and lung disease. Hemorrhages are extremely common either into the acini, staining the colloid, or into the interstitial tissues, sometimes with subsequent encapsulation and cyst formation. They are seen much more often in goitrous than in normal thyroids.

Atrophy occurs in advanced life, the senile form. It often accompanies wasting diseases, particularly tuberculosis, may be due to local pressure from tumors either within or outside the thyroid gland, and may be of unknown cause, especially in connection with such clinical conditions as *adiposis dolorosa*, endemic cretinism and myxedema. Grossly, the organ is usually small and underweight, and even although it may be of normal size or slightly larger, the connective tissue growth is extensive. The organ is firm and the capsule thickened. It cuts with increased resistance and shows a firm cut surface

which may or may not show lobular arrangement and contains little or no colloid. Histologically, there is more or less dense fibrosis of the capsule and of the stroma. In the atrophic thyroid of comparatively young individuals there may be a considerable vascularization, but in the atrophy of old age there is likely to be no increase of vascularization and considerable arteriosclerosis. Colloid is reduced or absent. Acini are small and irregular in size. The cells show a lack of uniformity in size and shape and occasionally, more particularly in young individuals, may be in several layers. The nuclei show lack of uniformity in size and some irregularity in shape, often with increased density of staining. More especially in atrophies of younger life, there may be local or diffuse accumulation of lymphoid cells.

Inflammations.—Gierke distinguishes between thyroiditis, if the gland be otherwise normal, and strumitis, if the gland be the seat of goiter. Acute diffuse thyroiditis occurs especially in relation to infectious and septicemic diseases but may rarely occur without known cause. The gland is likely to be swollen, hyperemic and tender or painful. Microscopically, there is a variable amount of exudation into the interstitial tissue, which may be largely fluid or largely cellular in character, and is accompanied by degeneration, desquamation and necrosis of the epithelium. This inflammatory lesion is not to be confused with the acute hyperplasias which also are likely to occur as an accompaniment of infectious disease. Acute focal thyroiditis is usually in the form of single or more commonly multiple abscesses, occurring in connection especially with septicopyemias. Abs-

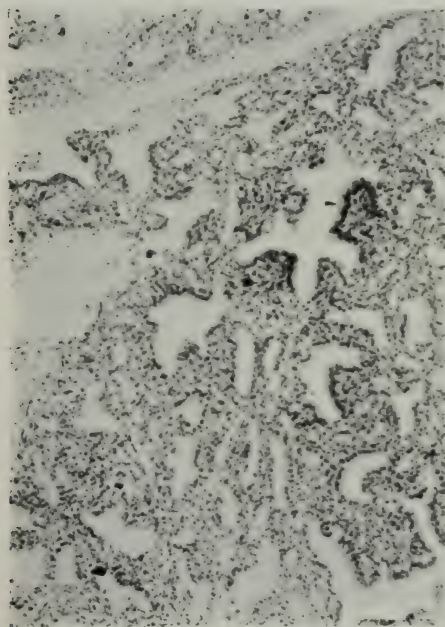


FIG. 377.—Thyroid hypertrophy and hyperplasia in a case of exophthalmic goiter.

cess may also arise by extension from the neighborhood of the thyroid or from the thyroglossal duct.

Features indicative of chronic inflammation are not infrequently observed. These, however, should not be confused with hyperplasia of the lymphoid apparatus of the thyroid, which may accompany generalized lymphoid hyperplasia. There may, however, be scars of old lesions or more diffuse overgrowth of connective tissue, with or without lymphoid infiltration, presumably indicative of a chronic inflammation.

The ligneous thyroid or *eisenhartes struma* of Riedel is in our opinion a chronic inflammatory process which justifies the term chronic productive thyroiditis. The thyroid may be of normal size but is more commonly a large, hard tumor-like mass, often with chronic inflammation of neighboring

tissue. Microscopically, there is diffuse and extensive fibrosis associated with infiltration of lymphoid cells and also plasma cells and eosinophiles. Although in the early stages there may be some epithelial hyperplasia, finally there is more or less marked destruction and disappearance of the epithelium. Not infrequently the epithelium shows irregularity of growth which suggests cancer. The cause is not known but Meeker suggests that inflammation of pharynx or trachea may be primary in some cases and offers the hypothesis that the lesion is particularly likely to develop in glands of low vitality.

Infectious Granulomata.—The commonest form of tuberculosis is miliary, which frequently occurs in connection with acute generalized miliary tuberculosis (Mosiman). Microscopically, the tubercles are situated especially in the connective tissue. Conglomerate tuberculosis usually develops as the result of extension from a neighboring focus, particularly the cervical lymph nodes. Occasionally, cases are encountered in which the primary focus of

FIG. 378

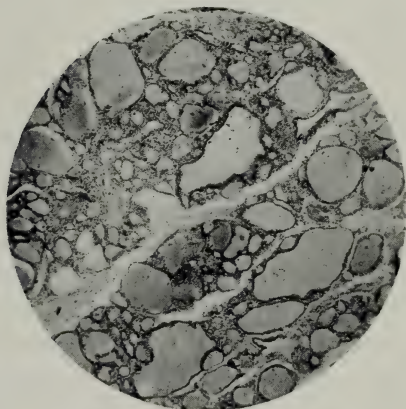


FIG. 379

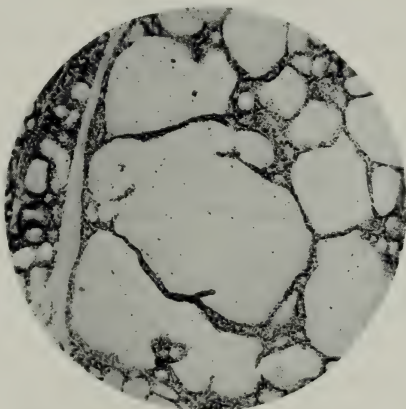


FIG. 378—Colloid goiter in the resting stage.

FIG. 379—Colloid goiter in the resting stage, showing spur formation.

tuberculosis cannot be clearly identified. Care must be taken in histologic examination to differentiate between tubercles and pseudotubercles. As the result of destructive lesions in the thyroid, pseudotubercles may be encountered with foreign body giant cells formed in response to the presence of dead cells and free colloid. In acquired syphilis, gumma of the thyroid may be observed (Davis, Senear), or there may be a diffuse fibrosis. In congenital syphilis there may be a diffuse mononuclear infiltration or gumma formation.

Hypertrophy and Hyperplasia.—The thyroid apparently is susceptible to a cyclic series of changes which are initiated by conditions that impose added work on it. The immediate result, really the first change in the cycle, is hypertrophy, which is closely followed by, or associated with, hyperplasia. In practical experience these two conditions go hand in hand. When the gland returns to the resting state it is no longer a normal gland but one which contains increased colloid, larger acini and lower cuboidal epithelium. That is, it represents some degree of the condition spoken of as colloid goiter. In fact, the term goiter is now restricted to changes occurring in this cycle. With

repeated cycles of hypertrophy and hyperplasia, fibrosis is likely to become more and more marked. Physiologically, there may be an enlargement of the thyroid at puberty, in the menstrual period, during pregnancy and sometimes at the menopause. Other than this, the examples of thyroid hypertrophy and hyperplasia, or goiter, are commoner in comparatively early life and in females, but may occur at any period of life and in both sexes. Much study has been given to the cause of goiter. In endemic form it is likely to exist in certain regions of the earth, as for example in and around Switzerland and around the Great Lakes in the north American continent. There are, however, numerous other areas, usually small in extent, in which the lesion may be very frequent. Many theories have been advanced to account for the condition. It was thought for many years that the high content in lime salts of certain waters was responsible for the disease, but experimental work has shown that this is not true. It has been thought by many to be of infectious origin but no experimental support can be offered to prove this contention satisfactorily. The most widely accepted hypothesis to-day is that offered by Marine and Lenhart and their collaborators, which indicates that deficiency of iodine in the water and in the food is responsible. Both experimentally and clinically this has been given extremely strong support. McCarrison has offered the hypothesis that intestinal disturbances may produce goiter, and has recently further elaborated this with the explanation that the intestinal disturbance prevents the proper absorption of iodine, even though it be present in the food and water.

The first stage of the process which leads eventually to the formation of a hyperplastic gland is simple hypertrophy, which, however, is rarely observed in practical experience (Graham). It is stated that the enlarged thyroid of puberty, that of menstruation and of pregnancy, and of the menopause, are examples of simple hypertrophy. The gland is enlarged and heavier than normal, but much of this increase in size and weight may be due to hyperemia. Histologically, the gland follicles are larger than normal and the lining epithelial cells become high cuboidal and then columnar in type.

Hypertrophy and hyperplasia are characterized by changes which vary considerably in degree, and no strict correspondence is to be found between the clinical symptoms and the degree of hypertrophy and hyperplasia. In fact extensive hyperplasia may exist without clinical signs other than the enlargement of the gland. Marine and Lenhart distinguish two groups of hyperplasia, namely the primary and secondary types. The primary hyperplasias arise in a gland which previous to the time has been normal, whereas the secondary hyperplasias arise in the glands which have other pathological lesions, particularly those due to the cycle of hyperplasia and involution. Grossly, the hyperplastic gland is large, heavy but of normal shape. It is soft and richly vascularized. It cuts with increased resistance and shows a slightly bulging, soft, red, cut surface whose translucency depends materially upon the degree of hypertrophy and hyperplasia and the degree of disappearance of colloid. The capsule and supporting connective tissue are overgrown. All these

changes, however, depend for their manifestations upon the degree and duration of the lesion. Microscopically, the changes are usually diffuse in the primary hyperplasias, but may be more circumscribed and accompanied by various secondary changes such as calcification, hemorrhage, cyst formation and increase in colloid, in the secondary hyperplasias. There is usually a connective tissue increase with more or less infiltration of lymphoid cells. Although this is sometimes interpreted as an indication of chronic inflammation, it is more probably a part of a general lymphoid hyperplasia which frequently accompanies the disease. The blood vessels are enlarged, hyperemic, elongated and tortuous. The acini are large and the lining cells thrown into more or less prominent plications depending upon the severity of the process. The cells in the early stages are high cuboidal but finally become cylindrical. The colloid in the stained sections is at first pale, then vacuolated and then disappears.

The colloid gland, or colloid goiter, represents the quiescent or resting state of the thyroid gland after it has undergone hypertrophy and hyperplasia one or more times. Grossly, it resembles a normal gland in many respects but is usually larger, heavier and contains a greater quantity of colloid. It is likely to be a firm gland with a somewhat thickened capsule. It cuts with increased resistance and shows a brownish-red, glossy, translucent cut surface, due to the increased amount of colloid, and as a rule the acini can be discerned with the naked eye as tiny, round, translucent, light brown gelatinous beads. Microscopically, the capsule and connective tissue show variable degrees of fibrosis. The arteries and frequently also the veins show residual thickening of the walls, often with calcification, and there is likely to be an obliterating endarteritis. Most of the acini are considerably larger than in the normal gland, and the residuum of the plication of the hyperplastic state is seen as spur-like projections into the acini. The cells have returned to the normal cuboidal state, the acini are filled with colloid which stains well and contains considerable quantities of iodine. The colloid may, in this condition as in others, and indeed in normal thyroid, show a scalloping of its edges near the cells, a condition long thought to be artefact. Uhlenhuth points out that they are vacuoles, probably of the same nature as the Anderson vacuoles, within the cells, and are "structures characteristic of living thyroid gland."

Recognizing the fact that these cyclic changes are likely to be repeated, it is not to be wondered at that the same gland may show various stages of the entire process. In the thyroid, as in other glands, there is often difficulty in distinguishing between hyperplasia and adenoma. In fact, glands occur in which the acini may be very large and there may be irregularity in form and disposition, sometimes associated with the formation of numerous small adenoma-like masses. Such glands are frequently referred to as the *diffuse adenomatous goiter* or diffuse colloid adenomatous goiter. This lesion occurs practically only in adult life. It appears to start in one or both lateral lobes near the trachea, as a clump of adenoma-like masses, and may finally involve the whole gland. This is the type of lesion which gives rise to very large

goiters and is the one which most commonly causes symptoms of pressure on the trachea. Histologically, there are usually considerable fibrosis, various vascular changes, areas of colloid goiter, areas of hypertrophy and hyperplasia, minute adenomata often poorly defined, and larger similar masses well defined, with compression atrophy of neighboring thyroid tissue. Hemorrhagic or glandular cysts may occur.

Regeneration.—If part of the thyroid be removed or destroyed, the changes in the remainder depend upon its bulk and functional capacity. A large gland is not necessarily more useful to the organism than a smaller gland, but it must be capable of fulfilling the functional needs. If, therefore, demands made upon a remaining portion of the gland be sufficient, hyperplasia

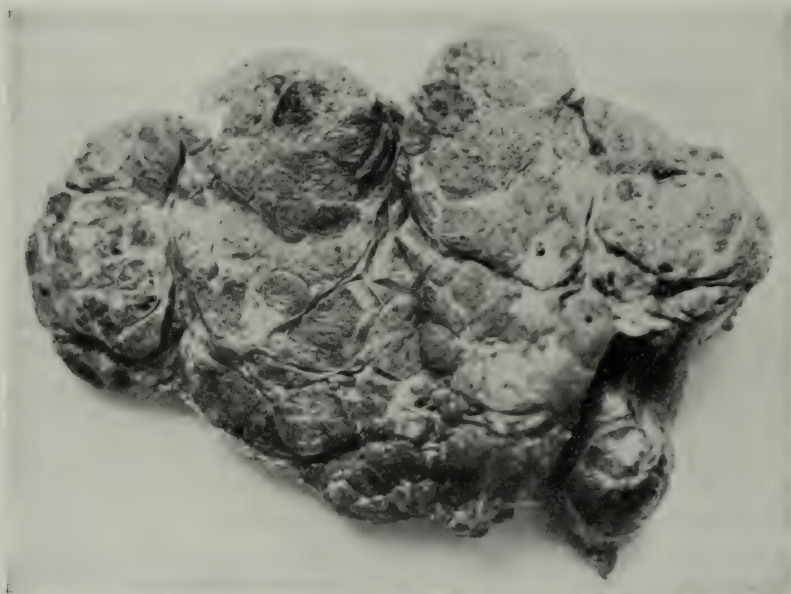


FIG. 380—Cut section of diffuse adenomatous goiter.

supervenes. This may or may not result in enlargement, but shows histologically the changes seen in hyperplasia and is to be regarded as regeneration at least in the functional sense.

Tumors.—In the consideration of this subject it must be borne in mind that the material presented here is a mere outline of the outstanding tumorous conditions. Fairly typical pictures may be given but departures from these are extremely frequent. Furthermore, the anatomical character of the thyroid is such that considerable difficulty is often encountered in diagnosing tumors. Indeed, even metastases of malignant epithelial tumors of the thyroid may so resemble normal thyroid as to make distinction extremely difficult. As Marine and Lenhart point out, the tumorous growths do not respond in the same way to iodine as does the thyroid gland, and this fact may aid materially in differentiating between hyperplasia which, in the course of a

few weeks undergoes regression by the administration of iodine, and adenoma which does not.

Various forms of adenoma are encountered. That which is most clearly a tumor is the one called fetal adenoma. This tumor usually appears in early adult life. It may be single but is not infrequently multiple. It may be situated in any part of the gland. When it attains a sufficient size it produces a nodular outgrowth on the thyroid and by pressure may lead to atrophy of the neighboring gland substance. It is an encapsulated, sharply defined, relatively soft, reddish-gray mass which projects slightly in the cut surface and is practically free of colloid. Some forms of this tumor, however, show moderate amounts of colloid. Histologically, it is made up of a large number of very small acini, free of colloid and lined with either cuboidal, high cuboidal or low columnar cells. There are minute fibrous septa running through the tumor, which support numerous blood vessels. Hemorrhage is a common complication and the blood may be absorbed and replaced by connective tissue which rapidly undergoes hyalinization. New alveoli grow into the hyaline mass. Quite similar tumors may show larger alveoli with lower epithelium and a stainable colloid content. Admitting that the fetal adenoma probably is derived from embryonal remnants of epithelium, lying between the normally developed acini, it is still an open question as to whether the adenomata of this type which contain colloid represent a resting stage of a cycle which takes place in the adenoma, similar to that in the thyroid gland as a whole, or whether they represent a further differentiation, both morphologically and functionally, of the cells composing the primary strictly fetal type of adenoma.

In addition to the fetal adenoma is the type called by Marin and Lenhart the simple adenoma which, we believe, corresponds with that adenomatous hyperplasia discussed in connection with diffuse adenomatous goiter. Usually there are multiple nodules made up of irregularly sized and shaped acini with low cuboidal epithelium and colloid content.

In either of these instances it appears necessary that some form of hyperplasia affect the gland before the adenoma develops. This inference is reached by the fact that it is only rarely that fetal adenoma occurs in a gland otherwise normal, and practically never does the simple adenoma occur in a normal gland. The fetal adenoma does not respond to the administration of iodine, but

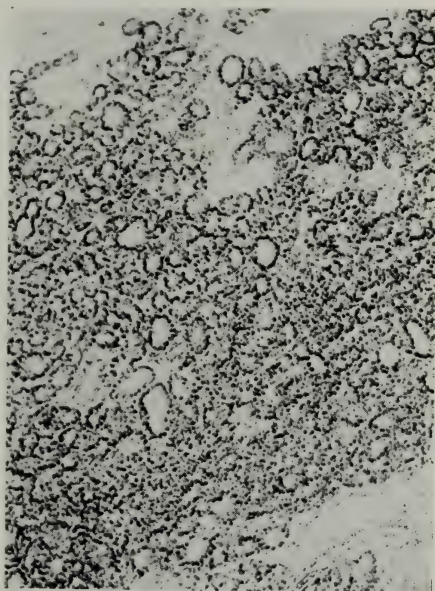


FIG. 381—Fetal adenoma with slight differentiation to small colloid acini.

in occasional instances the administration of iodine may bring about involution of the simple adenoma. Therefore, this latter condition is probably in many instances more closely related to hyperplasia than to true tumor formation. Kline holds the view that such adenomata, and perhaps those of fetal type, develop from the adult gland which has at some time been hyperplastic.

Other adenomatous masses may be encountered in the thyroid. Thus, an adenoma composed of large cells and small alveoli is supposed to be derived from the postbranchial body, and constitutes the struma postbranchialitis of Getsowa. Apparently this is disposed to undergo malignant transformation in

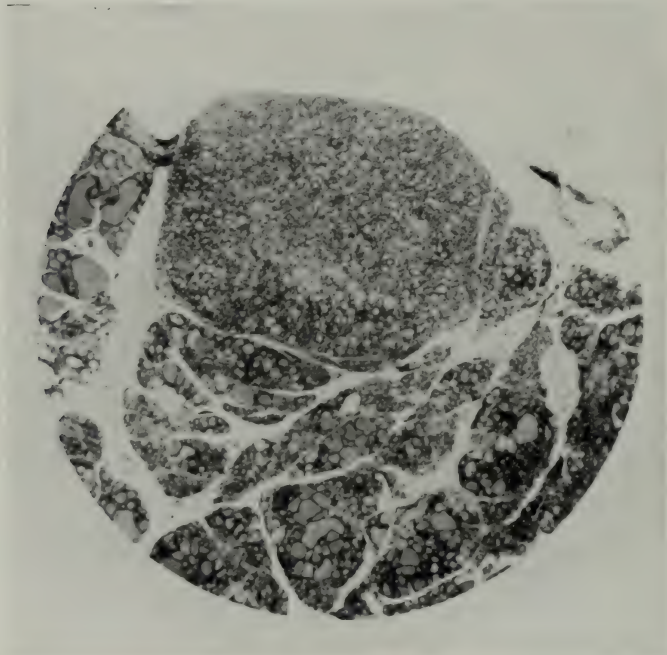


FIG. 382—Microtessar photograph of a simple adenoma of the thyroid.

its course (Richardson). Somewhat similar are small adenoma-like masses of tissue resembling the parathyroid gland, usually spoken of as parastruma.

Any attempt at classification of carcinoma of the thyroid encounters many difficulties because of the wide variation in histological picture, and also because of the fact that tumors which histologically give no indication of malignancy may metastasize widely (see Wilson, also Müller and Speese). Grossly, the carcinoma is usually a fleshy, relatively soft, richly vascularized invasive tumor with adhesions to surrounding parts. Microscopically, there is usually no difficulty in distinguishing the papilliferous adenocarcinoma and the scirrhous carcinoma, and the same is true of most cases of carcinoma simplex or as it is often called, carcinoma solidum. There is, however, a group of cancers of the thyroid which we may call, for simplification, the adenocarcinoma. This includes the outspoken adenocarcinoma, the malignant adenoma, and a variety of other adenomatous lesions in which the histological

picture may be extremely varied. Thus, thyroid glands may be removed which histologically may show the picture of fetal adenoma, the more highly differentiated or simple adenoma, hyperplasia and hypertrophy, as well as atrophy, but which show nothing clearly indicative of malignancy; yet in such cases tumors may recur after removal, or distant metastases may develop. Furthermore, histological examination of the metastases may show nothing clearly indicative of malignancy other than their situation. The careful and exhaustive studies of Graham make it seem likely that the diagnosis of malignancy in these cases can be made in most instances by careful gross and meicroscopic examination of the blood vessels. In this type of case he has been able to find invasion of the blood vessels in practically all. The metastasis of malignant thyroid tumors is often to bone, lung, and other similar situations where blood transport seems the most likely method. The papillary adeno-carcinoma and the scirrhou carcinoma, and in many instances also the carcinoma simplex, metastasize through the lymphatics to the regional lymph nodes.

It seems likely from the studies of Graham that many of the cancers of the thyroid are derived from preëxisting fetal adenoma. Most of the

patients suffering with cancer give a history which indicates that they have had some preceding lesions of the thyroid, either in the form of adenoma or of hyperplasia and hypertrophy. Nevertheless, it seems possible that some of the cancers originate in glands otherwise normal. The fact that cancer is more frequent in goitrous districts than in others would indicate the probable significant relationship of goiter.

The connective tissue tumors of the thyroid are much less frequent than are the epithelial tumors. Occasional cases of fibroma and osteochondroma are reported. Sarcoma may occur as a spindle cell sarcoma or a round cell sarcoma. Ewing, however, points out that in the growth of carcinoma the relationship between epithelium and stroma may be such that the epithelial cells become elongated and of spindle form. It is probable that a careful

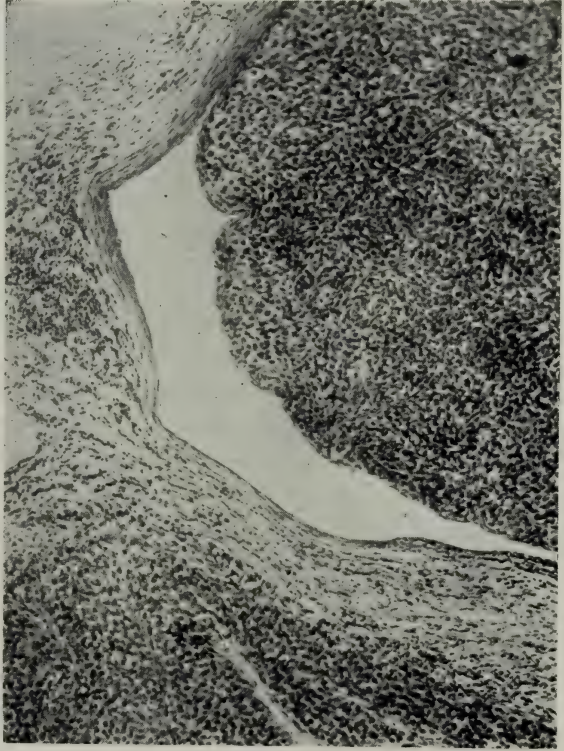


FIG. 383—Carcinoma simplex of the thyroid with a tumor mass in a vein.

study of many cases heretofore called spindle cell sarcoma might show that they belong to the group of carcinomas. It is equally difficult to distinguish between the large round cell sarcoma and an epithelial tumor. The same is true of the small round cell sarcoma, because under certain circumstances the epithelial cells of the thyroid may be small. It is probable, however, that there are distinctive cases of lymphosarcoma of the thyroid. More highly differentiated sarcomas, such as the osteochondrosarcoma are rarely observed.

The mixed tumors of the thyroid include particularly the carcinosarcoma, several of which have been reported. In view of the difficulty just indicated regarding the diagnosis of sarcoma in the thyroid, it is even more troublesome to be able to state with assurance that the same gland is the seat of both carcinoma and sarcoma. True teratoid tumors of the thyroid gland occur but are extremely rare.

Cysts.—Although the acini of the thyroid may be much enlarged, they rarely if ever constitute large cysts. Follicular cysts are due to hemorrhage into the follicles. They are usually small but may attain a diameter of six or eight centimeters. They contain more or less colloid, mixed with blood in various stages of degeneration, and often cholesterol. The capsule is made up of the wall of the follicle to which in the larger cysts are added connective tissue stroma of gland and gland capsule, with new connective tissue produced in response to pressure and irritation. Adenomatous cysts are due to necrosis in the center of an adenoma, usually followed by softening and hemorrhage. They contain a granular fluid material stained with blood or brown hemogenous pigment and little or no colloid. Later the fluid may be clear and of yellow or pale green color. The wall is made up of the peripheral parts of the adenoma and its capsule, or the latter alone, and the neighboring gland is compressed and atrophic. The walls of both varieties often contain areas of calcification.

Echinococcus cysts have been reported.

Physiological Considerations.—The thyroid is not necessary for life, but if absent, there occurs cretinism or myxedema. Marine, Lenhart, Kimball and others have demonstrated the significance of iodine for thyroid activity. Apparently thyroid hypertrophy and hyperplasia are due to deficient amounts of available iodine, for if iodine be administered the glands undergo involution. Similarly, in districts where goiter is prevalent, the administration of iodine prevents its occurrence. Kendall has isolated an iodine bearing complex from the thyroid, thyroxine, which is believed to represent the hormone of the gland. Its administration relieves the symptoms of athyreosis and in normal individuals may produce many of the symptoms associated with excessive thyroid activity. Uhlenhuth points out that the inorganic iodine is necessary for rendering available the hormone of the gland. Hypothyroidism produces cretinism of the young or myxedema of the adult. The term hyperthyroidism is applied to a state of increased nervous excitability and metabolism, as well as to exophthalmic goiter. In both of these, however, it is difficult to be sure that the thyroid is either primarily or solely at fault. In both hypothyroidism

and hyperthyroidism there are important changes in the autonomic mechanism, in metabolism, in muscular and mental activity. Admitting that all may be due to increased thyroid activity, it is also possible that this activity is due to alterations in the autonomic nervous system or that it is but part of, and secondary to, a widespread disturbance of the nervous system and ductless glands. In adults it is not uncommon to find coincidentally, changes indicative of both decreased and increased thyroid function.

Cretinism.—This is a condition of early life characterized by delay in the development of bones, often with dwarfism, delayed dentition, reduced metabolism, retarded mental development which may be a state of idiocy, so-called cretinistic facies and myxedematous skin. It is presumably due to deficient thyroid hormone and may occur as sporadic cretinism, often called congenital myxedema, and endemic cretinism. The sporadic form may be encountered anywhere and usually has as its base congenital aplasia or hypoplasia of the thyroid. Endemic cretinism occurs principally in goitrous districts, develops as late as the fifth year, is less amenable to relief by administration of thyroid and often shows a large thyroid, although aplastic or hypoplastic glands may be found. The large thyroids may show hypertrophy and hyperplasia, colloid goiter, adenoma, and diffuse adenomatous goiter. Nevertheless, it seems probable that in spite of the anatomical conditions, the thyroid is deficient in function. The bones often show a persistence of epiphyseal cartilage for long periods after maturity. Other disturbances of bony development may apparently be of cretinistic variety, as for example, certain cases of chondrodystrophia fetalis (Symmers and Wallace), although in most instances it is independent of thyroid disease. Deterioration of hypophysis and gonads are often found in cretinism and may be observed in adults deprived of the thyroid (Wegelin).

Myxedema.—This term is usually applied to adult cases of thyroid hypofunction, although some authors refer to sporadic cretinism as congenital myxedema. In the adult the bony changes of cretinism do not occur and the curious non-pitting swelling of the skin is often a most prominent feature. This type of edema is due principally to the deposit of mucoid in the corium and subcutaneous tissues. There are dryness of skin, loss of hair, dull heavy facies, "spade hands," chilliness, decreased metabolism, dull mentality sometimes with dementia, secondary anemia, leucopenia with relative lymphocytosis and other signs and symptoms in variable degree (Phillips). Characteristically, the thyroid is the seat of atrophy and fibrosis, but grossly may be of considerable size. Occasionally, the entire thyroid is removed surgically, and myxedema follows. Late in the course of exophthalmic goiter or other similar conditions the gland apparently reaches a stage of exhaustion, and the patient while still suffering from many symptoms of hyperthyroidism shows also signs of myxedema. The gland in such instances is often the seat of interlobular and interacinar fibrosis, and the parenchyma shows lack of uniformity in size of cells and of nuclei, some of the latter being large and deeply chromatic. Mitotic figures and multinucleated cells are not infrequent. Both

cretinism and myxedema are benefited by administration of thyroid gland. Sometimes relief is not complete, which Wegelin explains as due to failure to correct the associated defects in hypophysis and gonads.

Exophthalmic Goiter.—This syndrome, often spoken of as Parry's disease, Graves' disease or Basedow's disease is one of early adult life and confined to the human race, especially women. There are enlarged thyroid, exophthalmos, tachycardia and muscular tremor. The exophthalmos is associated with other more or less characteristic signs, such as lagging of the upper lid, infrequent winking and decreased power of convergence. The skin is warm and



FIG. 384—Cut section of a hyperplastic thyroid of exophthalmic goiter.

moist and may show areas of depigmentation, the patients often feel warm, the metabolism is increased, the patients are mentally excitable and may become delirious, blood pressure is normal or slightly elevated, micturition is frequent, hyperglycemia and glycosuria are common (Geyelin), there is muscular weakness and usually decrease in sexual excitement and power. In addition to tachycardia, other cardiovascular disturbances occur (Kerr and Hensel). It becomes at once apparent that this disease causes widespread disturbance in the body, and certain observers emphasize

the importance of the autonomic nervous system and regard the thyroid derangement as secondary (Kessel, Hyman).

The pathological changes in the thyroid are by no means constant. The larger number of cases, as in the studies of Marine and Lenhart and of MacCallum, show hypertrophy and hyperplasia, large soft or firm, hyperemic glands with the usual picture microscopically, mild or slight fibrosis and often outspoken lymphoid hyperplasia. The picture varies depending upon whether the hyperplasia is primary or recurrent (secondary). Some patients, however, show pure colloid goiter, some show premature atrophy, and others show fetal or simple adenoma. In a few cases the gland may be normal as regards gross and microscopic structure and iodine content. In these, however, the patients are likely to have all the signs and symptoms of exophthalmic goiter except exophthalmos. The hyperplastic glands characteristically show decrease of iodine content. Recognizing that in goitrous districts the thyroid is likely to

show many changes, exophthalmic goiter in the same districts often shows a complicated picture (Marine). The thymus, especially the cortical part (see Roussy and Huguenin), spleen and lymph nodes are often the seat of hyperplasia. The heart is often the seat of hypertrophy, but histologically there may be foci of necrosis as observed by Goodpasture and produced experimentally by him with thyroxin, or the heart may show areas of fibrosis, presumably scars of the acute lesions. The large vascular trunks to and from the thyroid may be dilated and hypertrophic. The liver cells are degenerated and may be necrotic, and the perilobular connective tissue may be so much increased as to constitute atrophic cirrhosis. Skeletal muscle may be atrophic and the bones are sometimes the seat of imperfect calcification, or a true osteomalacia. It is probable that the exophthalmos is due to spasm of the smooth muscle fibers of Müller, but if the condition persist, there may be a deposit of fat in the orbit.

Hyperthyroidism.—Numerous patients with or without goiter exhibit groups of symptoms mentioned under exophthalmic goiter. Such patients are usually older than those with exophthalmic goiter and may have had simple goiter for years. The symptoms may be severe, moderate or slight, and are ordinarily ascribed to increase of thyroid function and may closely resemble the symptoms following injections of thyroxin. If, however, exophthalmic goiter be regarded as a syndrome with its origin in the autonomic nervous system, it is possible that these less marked symptoms are manifestations of the same disturbance. The thyroid may show hyperplasia and hypertrophy or may show nothing to indicate attempts at increased function. In this category may be placed the so-called toxic adenoma. Some of the patients are victims of adenoma of the thyroid and, following the removal of the adenoma or adenomas, the symptoms may be relieved. This therapeutic test, however, is not entirely satisfactory, for the patients often have goiter for years before toxic symptoms occur, and many adenomas are never associated with general symptoms. Goetsch is of the opinion that even although the cells may be low cuboidal and without any indication of increased activity in the ordinary microscopic picture, yet the presence of large numbers of mitochondria indicates increased activity. It is somewhat doubtful that the number of mitochondria is an index of the secretion of hormones. The fact that Nicholson finds them increased in experimental compensatory hypertrophy, suggests that they might be related to cell size as well as to function or perhaps to size alone. Graham's experiments with tadpoles show that the microscopic picture of the adenomata bears no relation to their content of iodine, or presumably to their function. Janney offers the conception that the so-called hyperthyroidism or thyrotoxicosis represents an alteration of secretion, a dysthyroidism, rather than an increase of normal secretion, and that the symptoms are due to a thyrotoxin not identical with thyroxin.

Other Ductless Glands.—Clinically other ductless glands are probably involved in producing some of the symptoms and signs which may complicate the picture of thyroid disease. These include hypophysis, parathyroid, adrenals and gonads. Anatomically the thymus is enlarged and presumably the

seat of hyperplasia in 75 per cent. of exophthalmic goiter patients (Souques), and lymphoid hyperplasia is almost as frequent. Changes in the other ductless glands are less regular in incidence and in anatomic form.

THE PARATHYROID GLANDS

General Pathology.—The congenital anomalies of the parathyroids are not well known. Their absence is incompatible with life. Their position may vary widely and glands or cell clumps can be included in the thyroid. Congenital aplasia of the thyroid is not associated with absence of the parathyroids. Congenital syphilis may be accompanied by parathyroid hypoplasia. Atrophy may be the result of pressure, as by an enlarged thyroid, or the result of age. The infant's gland may contain only chief cells, but as life advances there may be an increase in oxyphile cells and increase of interstitial fatty tissue (Gierke). In generalized amyloidosis the vessels of the parathyroids may be affected. Hydropic infiltration and also necrosis occur.

Hemorrhage induced especially by difficult labor, is fairly frequent. The blood is soon encapsulated and may be entirely absorbed.

Metastatic abscess may occur in pyemia, miliary tubercles in a generalized tuberculosis.

Hyperplasias are not infrequent and are usually made up of the chief cells, sometimes with clumps of oxyphiles. The term *parastruma* is applied to both hyperplasia and adenoma.

Tumors.—The border line between hyperplasia and adenoma is hard to define, but fairly large tumor-like glands occur and, in the thyroid, aberrant parathyroid tissue may attain tumor-like proportions (Harbitz). Malignant tumors show invasion and even metastasis. In the adenoma the cells are in palisade arrangement, sometimes forming alveoli, and rich in glycogen (Ewing). In the malignant tumors the cells are less regularly arranged and may be multinucleated or show spindle forms. Occasionally, metastases of other tumors are found in the parathyroids.

Physiological Considerations.—The removal of all accessible parathyroid tissue results in death in a few days. If, however, calcium or parathyrin be administered and the symptoms be relieved, a compensatory mechanism of some sort is established, perhaps hypertrophy of other parathyroid tissue, and the patient survives. If destruction of parathyroid be gradual, as in the growth of metastatic tumor nodules, no symptoms occur (Thompson). Complete parathyroidectomy, untreated, leads to tetany and death. Some cases die without tetany in a state of presumed intoxication, said to be due to accumulation of poisonous materials that should be disposed of through the influence of the parathyroids (Harvier). *Tetany* is a condition in which there are muscular tremors and in which local or widespread convulsions may be set up by minor stimuli. Carnivora appear to be more susceptible than herbivora (Boothby). The increased excitability of peripheral nerves has been amply demonstrated, and this condition can be produced in the extremity of an otherwise normal animal by perfusion with the blood of a parathyroid-

ectomized animal. Loeb found that increased muscle and nerve irritability are due to decreased calcium ions. The studies of MacCallum and Voegtlin have shown that in tetany there is an increased output of calcium in urine and feces, associated with a reduction of the blood calcium. Conversely, Collip's parathyrin produces a marked elevation of blood calcium. Apparently, phosphates and chlorine are in inverse proportions to the calcium, and magnesium is generally parallel. According to Salvesen and Linder the diffusible ionized calcium is especially affected in parathyroidectomy. A primary alkalosis is ultimately replaced by acidosis as the tetany becomes marked. The parathyroids also appear to regulate the amount of guanidin in the body (see Wells).

All forms of tetany are not necessarily due to calcium decrease. Critchley describes eleven varieties of tetany and concludes that the condition is "essentially an intoxication by nitrogenous by-products" and that parathyroid upset occurs only in tetany parathyreopriva. Dragstedt believes that parathyroid tetany is a toxemia of intestinal origin. Uhlenhuth attributes it to the thymus. Barker opposes any particular unity of cause.

The relation of parathyroid to bone diseases has been extensively studied. Erdheim found changes in dentition and bone repair following parathyroidectomy. In rickets, hyperplasia of the parathyroids is commonly found (Pappenheimer and Minor, Doyle), and essentially the same condition of the glands follows prolonged feeding on calcium deficient diets (Luce). Hyperplasia has also been found in osteomalacia and osteoporosis (Todyo). Korenchevsky maintains that rickets and osteomalacia represent identical conditions. It is, therefore, possible that in the course of these diseases, deficiency of calcium leads to a sort of compensatory hyperplasia of the parathyroids. Although gland feeding is said to benefit paralysis agitans, Thompson found no morphological change in the parathyroids in this disease.

THE THYMUS

Congenital Anomalies.—The thymus may be congenitally absent in otherwise normal or in malformed fetuses. Accessory thymic nodules may be found near or in the thyroid. Congenital hypoplasia may be associated with myxedema. Hyperplasias may be congenital. Inclusions of thyroid and of parathyroid may be found.

Retrogressive Changes.—At birth the thymus is well developed, and although the body as a whole grows at a more rapid rate, the thymus continues slowly to enlarge until puberty, when involution begins. Some authorities believe that involution begins as early as the second year. The involution does not go to complete disappearance at any age (Hammar). Accidental involution is practically synonymous with atrophy (Wiesel) and may be due to general inanition, irradiation, vaccinations and a wide variety of acute and chronic infections, although the same conditions may sometimes produce hyperplasias. In normal involution there is a gradual reduction in the number of cells and of Hassall's corpuscles and a substitution growth of fatty tissue (Schridde). In atrophy the cortical cells show reduction in number and fatty

degeneration, followed by reduction of the medullary cells, which leaves the Hassall's corpuscles closer together. As the process goes on, connective tissue increases in amount and this may be so great as to produce the so-called sclerotic atrophy.

Cloudy swelling, fatty degeneration and foci of necrosis may occur in the thymus in acute infectious diseases. Calcification of Hassall's corpuscles is common and of no real significance.

Circulatory Disturbances.—Passive hyperemia is associated with general passive hyperemia and is prominent in birth asphyxia. Petechiæ occur in infectious diseases and in hemophilia neonatorum. Large hemorrhage, or "thymus apoplexy," is uncommon, occurs especially in infants and may be, but is not always, associated with sudden death. Wahl and Walthall believe that syphilis is a most important factor in its etiology but that other factors such as hemorrhagic disease, passive hyperemia, trauma and infections may cause the lesion.

Inflammations.—Swelling, hyperemia and cellular infiltration with degeneration or necrosis of the parenchyma, apparently an acute parenchymatous thymitis, may occur in acute infectious diseases. Abscess may result from infections of the new born or in later life and by direct extension from neighboring suppurations. The thymus may be so enlarged as to produce pressure upon the trachea. Chronic inflammations result in the progressive fibrosis of sclerotic atrophy.

Tuberculosis of the thymus occurs in generalized miliary tuberculosis and sometimes appears to follow caseous pneumonia. The mediastinal lymph nodes are also often extensively involved.

Syphilis.—In acquired syphilis gumma formation is rare. In congenital syphilis an interstitial fibrosis may be observed, sometimes with a diffuse lymphoid cell infiltration. Occasionally, syphilitic infants show the so-called Dubois abscesses of the thymus. These are single or multiple, smooth walled, well defined cavities, a few millimeters in diameter, which contain a puriform material. Schridde has found *treponema pallidum* in several such cases. These are regarded by many as an inflammatory dilatation of Hassall's corpuscles (Oliver), which Hammar speaks of as luetic sequestral cysts. On the other hand, Simmonds finds few Hassall's corpuscles and a marked proliferation of the medullary epithelial cells in the midst of which are the cysts which contain lymphoid cells, leucocytes and *treponemata*. Other authors consider the lesions as softened gummata.

Progressive Changes.—A distinction is to be made between persistence of the thymus and hyperplasia. Both may be associated with the condition known as status lymphaticus. The thymus involutes at or about puberty, if not earlier. A gland of normal size for a ten year old child if found in later life may represent a persistence or may be a hyperplasia of a gland which had undergone some degree of involution. Grossly, only those glands markedly overweight can be regarded as hyperplastic. Microscopically, the persistent gland shows a normal ratio and size of cortex and medulla. The hyperplastic

gland may show increase in number of cells of cortex and medulla, of medulla alone, usually with reduction of cortex, or of cortex alone, usually with reduction of medulla. Hyperplasia may occur in a variety of conditions but is particularly associated with exophthalmic goiter and with status lymphaticus. Regeneration follows partial removal in young animals (Marmorsten-Gottesman and Jaffe).

Status Lymphaticus.—This syndrome, also called status thymolymphaticus and status thymicolymphaticus, is a disease of early life, affects males more frequently than females, and is more frequent in white than in negro subjects. The syndrome includes thin smooth skin, large eyes, large lymph nodes, large thymus, hypoplasia of cardiovascular system, hypoplasia of sex organs and of the adrenal cortex, feminine type of secondary sex characters and minor anomalies of viscera. The thymus may be merely persistent, may be markedly hyperplastic with a weight of 70 or 80 grams or more, or may be partly involuted. The hyperplasia may affect the medulla (Schridde) or the cortex (Symmers). The corpuscles of Hassall often show necrosis (Pappenheimer). The spleen may or may not be enlarged. The lymph nodes are usually hyperplastic. Thus, the systemic and superficial lymph nodes, the lymphoid follicles of the entire alimentary canal, those of the liver, lung and bone marrow may show hyperplasia. In the microscopic examination a most noteworthy, if not truly characteristic, change is well described by Symmers. This consists of a hyperplasia of the germinal centers in spleen and lymph nodes, with marked cellular disintegration, disappearance of cytoplasm and prominent karyorrhexis. These areas subsequently become the seat of fibrosis. Apparently, the necrosis may recur again and again, for the same follicle may show both necrosis and fibrosis. The hypoplastic arteries, especially those of the brain, may rupture. The hypoplasia of adrenal cortex and indeed of the entire chromaffin system may be associated with Addison's syndrome.

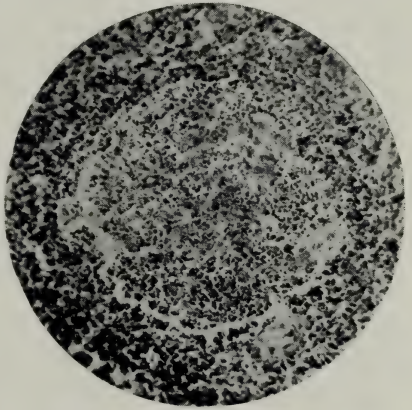


FIG. 385—A splenic follicle in a case of status lymphaticus, showing widespread necrosis of the germinal center.

Thymic asthma is believed to be due to pressure of the thymus upon the trachea and the dyspnea may be relieved by removal of the gland. If, however, the asthma be due to a hypothetical intoxication or nervous disturbance, the same curative effects might be observed. It is supposed that death may be due to tracheal compression but if this be true it is extremely rare.

The term thymic death refers to abrupt death in victims of status lymphaticus. Various explanations have been offered including tracheal compression, involvement of vagi, intoxication and anaphylaxis. The rarity of death from proven tracheal obstruction has been referred to. There are few,

if any, exact observations tending to support the idea of vagal lesion. The hypothesis offered by Symmers, that the body is sensitized by germinal center necrosis and is shocked by a subsequent necrosis, is not borne out by studies of the phenomenon of anaphylaxis, for this would be an iso-anaphylaxis, the existence of which has failed of demonstration. The lesions of the lymph nodes probably are the result of some general intoxication, the origin of which is not known, but which may be responsible for death. It is probable that patients with status lymphaticus are highly susceptible to intoxications, since it is well known that in them infectious diseases run a severe course and are often fatal.

Tumors.—Tumors of the thymus are infrequent. Lipoma, myxoma and thymic cysts are reported. The malignant thymoma is usually a large, smooth or slightly lobulated tumor which rarely invades the sternum, but commonly extends into the pericardial tissue through lymphatics. Metastasis, usually by way of the lymphatics, may be widespread. Histologically, the tumors may be made up of small round cells resembling lymphoid cells, larger cells with cell processes or bridges, outspoken carcinomas (Jacobson) or mixtures. Foot inclines to the view that all these are of epithelial origin and are carcinomas, but the small cell tumors may be regarded as sarcomas if the view be accepted that the small thymic cell is of lymphoid character. Kowalski regards the mixed cell tumors as essentially carcinomatous and explains the presence of the small cells, which he considers lymphocytes, as due to a chemotactic influence of the epithelial cells. Accepting the conception that the cells are epithelial, Schridde suggests that the small cell tumors be called cortical carcinomas and the large cell tumors, which may contain Hassall's corpuscles, medulla carcinomas. Jaffe and Plavska, however, regard the cells of Hassall's corpuscles as reticular and not related to the duct of Remak. Spindle cell sarcomas are rare. Metastasis of tumors to the thymus has not been reported, probably because at the age in which the thymus is large, malignant tumors are uncommon.

Dermoid cysts and simple cysts lined by ciliated columnar epithelium are probably derived from thymus anlage. Schridde expresses the view that the solid complex teratomas of the mediastinum are not derived from thymus or its anlage.

Physiological Considerations.—Experimental work on the thymus has led to conflicting results. The organ is not essential to life. Although Klose and Vogt described alterations in bones following thymectomy, Park and McClure working under carefully controlled conditions found no observable effects following excision of the thymus. Feeding thymus to tadpoles caused no alteration of metamorphosis. Uhlenhuth observed tetany in salamander larvæ when fed thymus before the parathyroids develop, and assumes that thymus contains a tetany producing toxic body which may be neutralized by the parathyroids. Hammar fed thymus to rats, and found that in young animals there is a delayed development of the testes and in adults degeneration of the testes. This is in keeping with the fact that puberty and thymus

involution are ordinarily concurrent. A relationship is similarly indicated by the observation of Kyrilow that the lipoids of the thymus are reduced during menstruation and after natural or artificial menopause. Marine, Manley and Baumann found that thyroidectomy hastens, while gonadectomy delays, involution of the thymus. Jaffe observed thymus hyperplasia in young and mature animals as a sequel of double adrenalectomy, which he believes is a manifestation of disturbed interrelation between gonads, thymus and adrenal cortex.

According to Crotti, Olkon observed muscular spasms and convulsions following intraperitoneal injections of thymus extracts, and Del Campo found that extracts relieve fatigue in nerve-muscle preparations. Riddle states that in pigeons thymectomy is followed by the production of eggs without shells, and feeding thymus to these birds is followed by development of shells. The organ in so far as it deals with calcification in mammals may be merely vestigial. The gland is often hyperplastic in exophthalmic goiter, and in such cases its partial removal may be followed by improvement of symptoms and decrease of relative lymphocytosis. In summary, it seems probable that the thymus may have some influence on calcium metabolism, may be responsible for toxic manifestations in thyroid and parathyroid disease and may be of importance in muscular activity, but in general its functions are not yet clearly demonstrated.

THE ADRENALS

Congenital Anomalies.—Severe malformations or absence of adrenals occurs almost solely in monsters, especially anencephaly (Kohn). In cases where they are apparently absent, careful search will disclose adrenal substance in other situations (see Miloslavich). In renal dystopia or aplasia, the adrenal retains the normal situation but may be of generally spherical form. The adrenals may be within the renal capsule. Heterotopia may also occur in the liver (Weller). Accessory adrenals may be found in various parts of the urogenital tract, as for example, the broad ligament (Warthin), in the lower surface of the liver or in the retroperitoneal tissues. These are usually made up principally of cortical substance. They are not uncommon, usually as single nodules, in the renal cortex near the upper pole. Hypoplasia of the chromaffin system is often associated with status lymphaticus (Wiesel). To be regarded as congenital anomalies are adenoma-like masses of cortical cells in the gland capsule.

Retrogressive Changes.—In infectious diseases there is a reduction of the lipid content. This may be widespread, leaving only fatty substance in the glomerulosa or islands in reticularis or fasciculata (Weisenfeld, Wülfind). Edema is also commonly present. Petechiae sometimes occur. In guinea pigs, inoculation with virulent diphtheria bacilli, or with toxin, produces characteristic changes in the adrenals, especially hyperemia, hemorrhage, reduction in lipid content and degeneration or necrosis of the cells. Amyloid occurs in cases of generalized amyloidosis. The organ is firm and gray. Microscopically, it shows the amyloid in the capillary walls between the cortical cells. The amyloid may involve the medulla and may lead to atrophy of the cortical

cells, may involve the medulla and may lead to atrophy of the cells. Cases of Addison's disease on the basis of amyloid adrenals have been reported. Atrophy of the adrenals may occur in old age or occasionally is observed in earlier life, and we have observed one case of Addison's disease with this as the essential lesion.

Frequently at autopsy the adrenals are found to have a much softened or semifluid, often dark brown medulla, which gives the organ a cystic character. This so-called postmortem softening, or pseudonecrosis is probably due to autolysis immediately after death, but Kraus and Sussig state that some sort of toxic injury in life is an essential prerequisite for this rapid autolysis.

Circulatory Disturbances.—Passive hyperemia accompanies general circulatory stasis. Active hyperemia occurs in many infectious diseases. Thrombosis of the vessels is sometimes seen. Extensive infarction may be the basis of Addison's disease (Furuta). Petechiæ occur in infectious diseases, marasmus, as the result of thrombosis or embolism, blood and hemorrhagic diseases. Petechiæ are common in the newly born. Massive hemorrhage is not rare, especially in early childhood, and may result from the diseases outlined above or from birth trauma (Corcoran and Strauss). The symptoms are those of internal hemorrhage. The lesion is not necessarily fatal.

Inflammations.—In septicemias and pyemias, abscesses may be found in the adrenals, sometimes followed by extensive cicatrization. An apparently progressive chronic fibrosis with contraction of the organ may be observed, especially in cases of similar disease in the kidneys.

Acute miliary tuberculosis as a part of generalized tuberculosis is frequent and of no demonstrable functional significance. Massive caseous tuberculosis, usually with more or less prominent fibrosis is less common but is the most frequent cause of Addison's syndrome. The lesion is usually bilateral and the organs are enlarged, nodular or smooth, may retain their general shape, and are often adherent to neighboring structures. They cut with increased resistance and show a gray, firm, cut surface with extensive, irregularly disposed caseation, the necrotic material being firm, dry and granular rather than soft or diffuent. Remnants of adrenal substance may be found. Occasionally, the fibrosis may produce contraction of the organ. In our cases some form of primary tuberculosis has always been found, but Gierke states that the lesion may appear to be the only tuberculous process present in the body, especially in congenital cases.

In congenital syphilis, spirochetes may be present in large numbers without histological lesion. There may, however, be diffuse round cell infiltration, cortical necroses, or gumma formation. In late, acquired syphilis, there may be diffuse fibrosis or gumma.

Progressive Changes.—Scott points out that in rats accessory cortical substance may undergo marked hypertrophy within four weeks, following adrenalectomy. Boycott and Kellaway found in rabbits no demonstrable hypertrophy of one adrenal after removal of its fellow, but this may be due to a presumably large reserve capacity, by which the remaining adrenal may

perform full function without need for enlargement. In man, the adrenal may be largely destroyed without any sign of hypertrophy in the remaining portions, even in well marked Addison's disease.

Tumors.—The adrenal adenoma is derived from the interrenal or cortical substance whether it be situated in cortex, as is usual, in medulla or capsule. It is usually small, only discovered microscopically, and may be multiple. Occasionally, a solitary large adenoma several centimeters in diameter is found. It is usually made up of vesiculated cells, arranged in cords, and in the larger forms is richly vascularized. Sometimes acinar structures are formed. The malignant tumor derived from cortical cells has been variously called hypernephroma, carcinoma, mesothelioma and suparenal epithelioma (Keyser and Walters). It resembles in gross and microscopic characters the hypernephroma of the kidney and may metastasize widely. Apparently, it occurs more often in childhood than in adult life, but is uncommon at any age.

The tumors of the adrenal medulla are those of the sympathetic nervous system. They are more common in children than in adults. These tumors have been discussed in the chapter on tumors and include especially the neuroblastoma, the ganglioneuroma, the neurocytoma and the tumor of chromaffin cells, the paraganglioma. Any medulla tumor may show mixtures of these types. The chromaffin paraganglioma may be associated with multiple neurofibromatosis. The neuroblastoma in which there is relatively little differentiation of cells is almost always malignant, and may show widespread metastases (Wahl). Bailey and Cushing have found that several such tumors originally classified as neuroblastomas are really medulloblastomas (see chapter on nervous system).

Tumors, more particularly those of cortical origin, may arise in accessory adrenal substance.

Benign tumors such as fibroma, lipoma, etc., are occasionally found in the adrenals. Secondary cancer and sarcoma nodules are occasionally found. Occasionally, in lymphoid leucemia and related diseases the adrenals may be much enlarged by the characteristic cell infiltrates.

Physiological Considerations.—The adrenal should be regarded as two organs, the cortex or interrenal substance and the medulla, the functions of which are different in many respects even though they may be interrelated. In many animals and probably in man, complete adrenalectomy leads to death in a few days. In others, notably the rabbit and rat, when adrenalectomy is properly performed, a considerable percentage survive for several weeks or indefinitely. Death at the end of a few weeks is apparently from adrenal cortex insufficiency. Whether or not the surviving animals have accessory adrenal substance adequate for a shorter or longer period of life is as yet unsettled, but it would seem that the burden of proof is on those who maintain that in such animals accessory substance is not present.

The studies of hyperfunction of the adrenals have been directed especially toward increases of epinephrin output. Cannon and his collaborators maintain that in emotional states, asphyxia, stimulation of sensory nerves, etc.,

the output of epinephrin is increased and correspondingly in some of these conditions the body glucose is mobilized. Many other investigators, working with the same and other methods, have confirmed the results obtained by Cannon. Rogoff, however, gives and quotes experiments which controvert these results. Although injections of epinephrin lead to hyperglycemia and glycosuria, Stewart maintains that in other experimental states produced by morphine, asphyxia, ether, piqure, etc., where there is hyperglycemia, increased output of epinephrin has not been demonstrated. In man much attention has been directed toward epinephrin as a cause of chronic hypertension. Although hyperplasia of the adrenal cortex is sometimes found in hypertension, this should have no influence upon epinephrin output and, as Hewlett points out, no increase of epinephrin in the circulating blood has been satisfactorily demonstrated. Hoskins, in his admirable review of the relation of the adrenals to circulation, shows that an amount of epinephrin sufficient to influence blood pressure would have serious by-effects, including paralysis of the intestinal musculature. Oppenheimer and Fishberg collected fifteen cases of adrenal tumor associated with hypertension. Of the tumors of medullary origin the chromaffin paraganglioma is the only one which appears to produce hypertension. Their own cases and several others are cortex tumors and the relationship to hypertension is difficult to determine. Some of these cases had glycosuria which might be interpreted as indicating increased epinephrin output. Although the hypertension is not of renal origin, there must be much doubt as to the relationship of the two conditions until the problem of hypertension is further unravelled.

Genetically and in certain other respects, including lipid content and reactions (Sorg and Jaffe), there is a relationship between adrenal cortex and sex glands. Cortical, and occasionally also medullary hyperplasia of the adrenals or accessory bodies, is sometimes associated with pseudohermaphroditism, more especially the female type with secondary male characters. When occurring in childhood, tumors of cortical origin, which in Glynn's series were distributed fourteen in females and three in males, are likely to show in the females the development of male secondary characters and in males precocity (see also Rolleston). Nevertheless, hyperplasia and adrenal adenomata are often observed without any such associated changes. As might be expected, hypernephroma of adult life is rarely if ever associated with sex disturbance. To quote Oppenheimer and Fishberg, "the triad of sexual precocity, obesity and development of heterosexual virilism are practically pathognomonic of hyperplasia or tumor of the suprarenal cortex, especially in girls, being differentiated from ovarian or pineal precocity by the heterosexual hair and from the obesity of pituitary lesions (Fröhlich's syndrome) by the sexual precocity."

When an animal dies as the result of adrenalectomy, the appearance of symptoms is abrupt, with fall of blood pressure, general weakness particularly in the hind legs, drowsiness and sometimes convulsions. Feeding of adrenal and injections of epinephrin have no effect other than that due to temporary elevation of blood pressure by epinephrin injections. In certain fish where

cortex and medulla are separate, the removal of the cortex alone leads to death (Biedl). Death is due then, to cortex deficiency rather than to lack of epinephrin. Stewart states that removal of the adrenal has no effect on the glyco-genic function of the liver. Nitrogen wastes may accumulate in the blood as a result of slow excretion by the kidneys (Marshall and Davis). Aub, Forman and Bright found a fall of basal metabolism in cats immediately following adrenalectomy. Marine found, in animals surviving longer, a rise of basal metabolism, which seems to depend upon cortical deficiency (Scott). Barlow, however, in an extensive study, obtained results similar to those of Aub. Marine found an increased production of hemolysins following adrenalectomy, but Ecker and Rogoff found no change in the production of precipitins or in resistance to tetanus toxin. Scott's observations on increased susceptibility to bacterial and other foreign proteins, depend probably upon some alteration of the mechanism of resistance to colloid shock, rather than to changes in immunity. It seems doubtful that the adrenals play any part in immunity.

Certain of the conditions which follow extirpation of the adrenals in animals occur in association with destructive lesions of the adrenals in man and form part of the picture of *Addison's disease*. Addison's disease is usually due to tuberculosis of the adrenals, but may also be due to atrophy, to tumors (Warthin), to infarction or to extensive amyloid infiltration. It may apparently be due to malformation (Wahl). It is said that Addison's disease may follow extensive destruction of chromaffin tissue other than that of the adrenals without significant disease in the latter. The principal signs are pigmentation of skin and of mucous membranes, especially of the mouth, asthenia and low blood pressure, sometimes accompanied by a variety of other signs such as vomiting, dyspnea on exertion, periodic breathing, all well discussed by Rowntree. The disease is more frequent in males and in later middle life, and although it may be prolonged, runs a course of about one year ending in death. Basal metabolism may be somewhat reduced, but muscle efficiency is normal and blood sugar is usually within normal limits. Although the kidneys secrete test dyes normally, there is often an accumulation in the blood of non-protein nitrogen, as in Marshall's animals. Rowntree recommends substitution therapy, but it is doubtful that real benefit is obtained. The relation between epinephrin, pyrocatechin and oxidizing ferments such as tyrosinase has been discussed in the chapter on pathological pigmentation. Rowntree's observations of reduced pigmentation under substitution therapy is suggestive, but too little is known of the course of pigmentation in the disease to draw final conclusions.

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CHAPTER XXI

ORGANS OF LOCOMOTION

BONES.
JOINTS.
SKELETAL MUSCLE.

BONES

Local Deficiencies of Growth.—Most of the anomalies of bone are referable to faulty growth rather than to defects originating in embryonal life. In rare instances aplasia of bones, more especially those of the extremities, may be attributed to embryonal faults, are true aplasias and represent congenital anomalies. Aplasia may also account for skull defects in monsters. The pressure of growing brain may presumably be responsible for fibrosis and failure of ossification, especially in the parietal bones near the interparietal suture. Defective bone formation occurs in many varieties of monsters. Single bones, as for example, the clavicle, may be absent. Entire limbs may be absent (amelus), or hands and feet may be directly attached to the trunk (phocomelus).

Referable to development in fetal life are those hypoplasias of bone which depend upon defects or injuries of the central nervous system, whereby the bones of an entire extremity may be small. Local disturbances of growth may be due to defects in epiphyseal or symphysis cartilage, or the connective tissue of cranial sutures. Similarly, premature calcification and fusion of these within the neighboring bone may inhibit development. In this general category are probably the cases of cleidocranial dysostosis, in which, often on a familial or perhaps hereditary basis, there is failure of ossification of the membranous cranial bones and of the clavicles (McCurdy and Baer). In fetal and postfetal life, inflammations and trauma to epiphyseal cartilage may lead to inhibition of growth and short diaphyses. Contractures of skin, following burns in early life, may prevent full development of bones, especially of the extremities.

General Deficiencies of Growth.—These include especially dwarfism, chondrodystrophia fetalis, osteogenesis imperfecta, cretinism and myxedema. Rickets and osteomalacia are classified as metabolic disturbances.

Dwarfism.—True dwarfism, independent of ductless gland disturbances, is rare. The individual is small in stature, with proportionately developed trunk and extremities but with large head. The epiphyses ossify later than normal, and according to M. B. Schmidt growth may continue slowly to the thirtieth year or later. In an apparently true dwarf, Talbot reports a marked increase of basal metabolism. Brain development and mentality are usually normal. In some instances heredity appears to play a part (Kraft). As has been indicated in the chapter on ductless glands, dwarfism may be due to disturbances of pituitary and thyroid. The cases reported by Mau appear to

be due in one instance to congenital syphilis of the pituitary and in the other to removal of the thyroid for goiter at three weeks of age. In adult dwarfs of this general type Staehelm and Gigon found normal metabolism. Early disturbance of the kidney may be associated with dwarfism (renal dwarfism, Barber, Patterson). Dwarfism may be due to achondroplasia, rickets and other bone diseases.

Chondrodystrophia Fetalis.—This condition has been variously called achondroplasia, micromelia chondromalacica, hereditary deforming chondrodysplasia, multiple cartilaginous exostoses. It is a disease which may originate at various periods of early intra-uterine life and involves endochondral bone formation. It therefore affects the extremities, which are short and often irregularly bowed, and the base of the skull with depression of the bridge of the nose. The trunk may attain full growth, and mentality and sex development are unaffected. The cartilage is not like that of rickets, there are no determined lesions of ductless glands and the disease is not cretinism (Goldthwait, Painter and Osgood). Kaufmann distinguishes three types. In chondrodystrophia hypoplastica, the cartilage is underdeveloped and seems incapable of proliferation, but is otherwise normal. In chondrodystrophia malacica or chondromalacia fetalis, similarly underdeveloped cartilage is soft in consistence. In chondrodystrophia hyperplastica the cartilage is larger than normal and may constitute massive nodular, irregularly ossified projections about the bone ends. In this condition the term multiple cartilaginous exostoses is often employed (see Ehrenfried). The chief character of the cartilage is a loss of the row arrangement of the cells associated with growth of bones in the long diameter, to such a degree that the irregular disposition suggests chondroma. Cartilage may be found in irregular disposition in the marrow (Opie and Allison). Often, however, the cartilage at the diaphyseal end of the long bones is deficient. Periosteal bone formation proceeds so that as a rule the bones are normally thick or may appear to be thickened. Curving of the extremities may be due to a greater longitudinal growth along one side of the bone than the other or, in forearm and leg, may be due to greater effect upon one bone than the other. The large head of the patients is usually due to an unexplained internal hydrocephalus (Dandy).

The studies of Underhill, Honeij and Bogert indicate that in the progressive stage of the disease there is a tendency to loss of calcium from the body, and that in both progressive and stabilized stages the magnesium output is increased.

No cause has yet been found for achondroplasia, but Jansen offers the interesting hypothesis that this condition and other forms of dwarfism are due to pressure by the amniotic sac.

Osteogenesis Imperfecta.—This disease is of fetal origin and is usually evident at or before birth, but, as indicated in Knaggs' extensive study, it may be first noticed in infancy, childhood, adolescence, middle life or old age. The fault is not in endochondral bone formation, as in chondrodystrophia fetalis, but in periosteum, endosteum, and in the fibrous osteoplastic tissues of

the flat bones of the cranium. It is often of familial distribution and may well be a hereditary defect. The long bones may and often do attain full length but the dense bone of the shaft is much thinner than normal. Even in fetal life the long bones show a striking disposition to fractures, called *fragilitas ossium* or *osteopsathyrosis*. The fetal fractures may heal with excessive callus formation and lead to marked deformity and shortening. The flat bones of the skull show deficient ossification and are soft or rubbery, with a few islands of bone formation. Kratzeisen can find no reason for assigning as the cause diseases of ductless glands, maternal nephritis, or syphilis, and points out that the disturbance is of fetal rather than embryonal origin. According to Knaggs the "osteoblast edging to the trabeculae is either absent altogether or only partially present in parts," and the fault lies probably in deficient osteogenesis rather than in excessive activity of the osteoclasts. In the region of the delicate cancellous tissue the cortical layer is absent and the periosteum is usually thickened. A blue gray color of the sclera of the eye is frequently present but the histologic structure is normal.

Although Bookman found a subnormal calcium retention in the disease, Klercker, and Schwartz and Bass found no alteration of the calcium or phosphorus metabolism, and Flagsted, Zanger and Leven report that in the blood the calcium, phosphorus, total nonprotein nitrogen, urea, creatinine and uric acid are within normal limits.

Cretinism. Myxedema.—These conditions have been referred to in the chapter on diseases of ductless glands. Cretinism often is associated with a peculiar type of dwarfism. The face is broad, round, with little expression, the forehead low, the lips thick and the bridge of the nose sunken. The fontanelles remain open for a long time; the spheno-occipital synchondrosis persists, leads to little ossification and thus produces the sunken nose. There is delay of endochondral bone formation throughout, and the epiphyseal discs are clearly visible up to the fifth or sixth year. Periosteal bone formation continues but the bones are either normal in form or more slender. Kaufmann describes cross striations at the diaphyseal border often visible in radiograms, which are probably due to a failure of osteoblasts to grow into the cartilage with a resultant transverse arrangement. When myxedema develops in early life, bone changes similar to those of cretinism may occur.

Increases in Growth.—These may be due to congenital influences such as in gigantism, or to disturbances which occur at later periods, such as akromegaly, chronic hypertrophic osteo-arthritis and leontiasis ossea.

Gigantism.—The difference between tallness and gigantism is not entirely an arbitrary measure of stature, although two meters (about 6 feet 6 inches) is set by Schmidt as the point beyond which gigantism may be said to occur. Occasionally, well proportioned individuals may be seen in excess of this height. As a rule, however, giants are distinguished not only by height, but also by disproportionate growth, in which arms and legs are long and skull small; in some cases the small head may be the only evidence of lack of proportion. The change is apparently due to excessive endochondral bone

formation, which may first be apparent at about the tenth year, and be complete at or somewhat later than the physiological period of growth. Muscles may be poorly developed and bone formation may be imperfect, with spinal curvature and genu valgum. Gigantism may be the sequence of castration in early life, and is attributed by some to removal of gonad antagonism to the activity of the pituitary gland. Akromegaly usually affects adults and, as will be seen, is different in several characters from true gigantism.

Partial gigantism may affect individual long bones as the result of irritation or hyperemia of the cartilage due to inflammations of bones or joints either pyogenic or tuberculous in nature, or to partial separation of the epiphysis (see Speed). If the process destroy the cartilage the reverse effect occurs.

Akromegaly.—Although akromegalics are often spoken of as giants, the condition of the skeleton is more in the nature of a hypertrophy or hyperplasia of some of the bones rather than a uniform overgrowth. The conformation of the face with its sloping forehead and overhanging eyebrows is due to an increase in size of the air sinuses, especially the frontals. The prognathism results from an increase in size of the maxilla due principally to periosteal bone formation. The same process is found in the long bones of the extremities, together with bony growth at the points of attachment of muscles and fasciæ. The general nature of the condition is discussed in the chapter on ductless glands.

Hypertrophic Pulmonary Osteo-arthritis.—This condition is most prominent in the distal phalanges of the toes and fingers and is uniformly symmetrical. The finger and toe ends are enlarged and bulbous and the nails rounded in both diameters, the skin and subcutaneous tissues thickened. The small bones of the phalanges may show no involvement, but may be the seat of a periosteal hyperplasia with new bone formation. More constant bone involvement is found in the periosteal ossification, either as a smooth lamella or in the form of nodular masses, upon the lower ends of the bones of the forearm and leg and sometimes the lower parts of the bones of the arm and thigh. The disease is secondary to other lesions such as chronic diseases of the lung including bronchiectasis, abscess, tuberculosis, empyema, and to prolonged cardiac decompensation, malignant tumors and syphilis.

Leontiasis Ossea.—Owing to a widely distributed thickening of the bones of the face, jaws and skull, the patients with this disease have the leonine face. The cause is entirely unknown, although Knaggs suggests bacterial infection. According to this writer there may be two types of bone involvement. In one there is a chronic periostitis, which begins near the region of the nose and spreads gradually to the bones of the face and skull. In the other type there is a chronic osteitis with great thickening so that the bones become ivory hard. In the flat bones of the skull the diploe may be thinned or entirely disappear.

Alterations of Nutrition. **Atrophy** of bones may be due to three processes. There may be lacunar resorption in which the bone becomes more spongy due to enlargement of the Haversian system, the so-called osteoporosis, often with enlargement of the marrow cavity. This is due to a loss of balance between the activity of the osteoblasts and osteoclasts, so that bone destruction proceeds

more rapidly than bone formation. Occasionally, atrophy is due to the penetration through the bone lamellæ, either from periosteum or marrow, of perforating canals which contain newly formed blood vessels. Whether the canal formation or blood vessel formation is primary is not known. The condition may heal completely. The third form exhibits an osteoid tissue poorly calcified and sometimes fibrous in character. This is said by some to be due to withdrawal of calcium salts from the bones, halisteresis, although others maintain that it is due to excessive activity of the osteoclasts. Atrophy may be eccentric or concentric. Eccentric atrophy begins in the marrow cavity and extends outward. Concentric atrophy begins at the periosteal side and extends inward.

According to Müller, atrophy may be endogenous, as for example senile atrophy, or exogenous as those forms due to pressure, to inactivity or to neurotrophic influences. In all forms the bones are likely to be brittle and unusually susceptible to fractures. Senile atrophy may affect the entire skeleton or may be confined to several bones. Thus, the long bones and vertebræ become porous and fragile. The bones of the face and flat bones such as those of the skull and also the scapula, show areas of decreased vascularity and thinning which may go on to perforation. The change is probably due to decreased osteoblastic activity. As in other senile changes, decreased muscular activity and arteriosclerosis are probably of importance. The so-called marantic atrophy is perhaps something of the same nature and occurs in starvation, as the result of diets deficient in lime and phosphorus and is common in experimental animals with fistulæ from the gastro-intestinal canal. Pressure atrophy is observed especially as the result of compression by tumors, by aneurysms and enlarging Pacchionian bodies in the dura. The skull bones may be thinned as the result of prolonged intracranial pressure of hydrocephalus. This is usually an increased porosity but may be a smooth wearing away of the bone surface. In the erosion of aneurysms there is often in addition a chronic inflammation which perhaps plays an important part in the atrophy. Pressure atrophy is probably due to increased osteoclastic activity. The atrophy of inactivity is observed in bones, particularly of the extremities, as the result of immobility from joint ankyloses, and is well seen in the stump of amputations where the bone may taper off markedly toward the cut end. This is often porous in type and in the amputation stump is concentric. Neurotrophic atrophy is observed in various bones; those of the lower extremities in *tabes dorsalis* and those of the upper extremities in *syringomyelia*. As a sequence of acute anterior poliomyelitis the principal change is a decrease of growth, although true atrophy may also occur. Whether this atrophy, as well as that observed in other forms of paralysis, is due to trophic disturbance or to inactivity is not yet settled. Both these forms of atrophy are probably due to decreased osteoblastic function.

Rickets.—Rickets or rachitis is a disease of early life characterized by disturbance of salt metabolism, especially of calcium and phosphorus, and by deficient deposit of lime salts in the bones. As concerns the bones, the disease affects the growing rather than the mature skeleton. Its first manifestations

usually occur at about the fourth month of life, but the time of its beginning is unknown. There is much doubt, however, that it begins in utero. It may develop at about the time of puberty, or somewhat later, when it is designated *rachitis tarda*. It is a disease of urban civilization, principally of Europe and North America, and is more frequent in the winter than in the summer. It appears among animals subjected to the artificial conditions of urban civilization but practically never when they are in the free state.

In children, even though they may be well nourished, the chief manifestations are square head with soft bones (*craniotabes*), corrugated teeth, enlarged costochondral junctions of the ribs (*rachitic rosary*), bowing of the long bones

and enlargement of the epiphysodiaphyseal junctions. Tetany is frequent. Infantile scurvy is said to be often accompanied by rickets, but in some cases this may be due to confusion of rachitic rosary with somewhat similar enlargement of the rib ends in infantile scurvy.

Although all the bones are softer than normal the striking changes are seen in the long bones. Those of the extremities are likely to be bowed. The ends are large and cartilaginous. A longitudinal section shows a large, poorly ossified epiphysis. The epiphysodiaphyseal junction is broad, poorly defined, with irregular margins and has a pale blue color. A large amount of spongy osteoid tissue is found near the ends, and sometimes throughout the shaft. The periosteum may be thick. The cortical bone is often thickened, but much less firmly calcified than normal. In ill-nourished children the epiphyseal enlargement may be in abeyance.



FIG. 386—Rachitic rosary, viewed from inside the thorax. A costochondral junction is cut longitudinally to show the rachitic metaphysis.

For the sake of clarity the microscopical changes are described as they affect the epiphysis and the shaft, although they progress coincidently. In the shaft the principal changes are poor calcification and the presence of an excess of osteoid tissue, especially near the ends of the shaft. In the latter there are the bone cells and a fibrous matrix without calcification. Osteoporosis with its rarefaction of bone, near the periosteum and bone marrow, and enlargement of Haversian canals, is common but is not a necessary feature of rickets. The enlargement of the epiphysis is not due to increased cellular proliferation but rather to a failure of absorption as bone formation proceeds. The parallel columns of cartilage cells near the diaphysis are disorganized and irregular, and the blood vessels growing in from the marrow are long and tortuous. The zone of provisional calcification in this area shows a striking decrease or complete

absence of deposit of lime salts, although immediately under the perichondrium there may be distinct calcification.

Following the fracture of rachitic bones, the amount of callus is greatly increased and, instead of normal ossification, osteoid tissue is found in large quantities.

Chemically the bones in rickets are deficient in calcium and phosphorus and contain an increased amount of water. No conclusions can be drawn as to the amount of these salts in the soft tissues. In the blood the calcium may be low and the inorganic phosphorus at or near normal, the inorganic phosphorus may be low and the calcium at or near normal, or both may be low. The deposit of salts in the bones, especially of the calcium, is not necessarily dependent upon the amount in the blood. Most investigators regard the state of the bones as due to inadequate deposit of salts rather than removal of lime from the bones, halisteresis. It is true that calcium deficiency in diets of experimental animals may lead to rachitic changes in the bones, and it is probable that the tendency of premature infants to rickets is due to inadequate calcium reserve in the body. Phosphorus deficiency may lead to the same changes. Nevertheless, rickets occurs when the amount of calcium in the diet and in the blood is normal. Experimentally rickets can be produced in animals by the use of diets adequate in calcium and phosphorus, provided the diet contain no antirachitic factor. Of further importance in calcification of bones is radiant energy in the form of actinic rays of sunlight and ultraviolet rays from artificial sources. The antirachitic factor occurs in abundance in cod liver oil and is present in various foods such as egg yolk and butter. The influence of sunlight is seen in the absence of rickets in the tropics even though the population is dark skinned, in the seasonal variation of disease incidence and in the cure of the disease by sunlight or ultraviolet irradiation. The interrelation between antirachitic factor and radiant energy is as yet unexplained, but that the relationship is probably very close is clearly suggested by the fact that antirachitic properties can be imparted to inert oils and other substance by irradiation.

For further details and references the reader is referred to the admirable articles of Korenchevsky, of Park and of Howland.

Osteomalacia.—This may occur in variable degrees of severity. The essential changes are softening of the bones, bowing of the extremities, scoliosis of the spine and deformity of the pelvis. It is a disease of adult life which affects man, some mammals and birds. White mentions three forms. A mild form occurs in women during late pregnancy, the puerperium or lactation, which is probably due to a severe drain on the calcium and phosphorus, not met by the diet. Somewhat similar is that which occurs in malnutrition such as was observed in central Europe following the Great War (Schmidt). Another mild form is that seen in advanced life, which affects especially the spine and pelvis. These forms tend to recovery, often with permanent deformity, when the cause is removed or dietary treatment instituted. The third form is steadily progressive and ultimately fatal. It occurs in pregnant,

puerperal or lactating women and may be the outcome of repeated attacks of the milder form. It also occurs in gonadectomized women and may occur without known cause in males.

Grossly, the spongy bones show increased porosity. The shafts show an enlarged cavity, and thinning and softening of the cortical parts. The red marrow is often hyperplastic. Fractures are not uncommon. Microscopically, there is a marked increase in osteoid tissue, in spongy bone and in the inner layers of the cortical bone (Bassett). Osteoporosis is also observed. The bones give the appearance of rickets as it might be expected to involve adult bone.

Experimentally osteomalacia may be produced in mature animals under much the same conditions as induce rickets. Both calcium deficiency and absence of the antirachitic factor appear to be highly important. The bones show much the same chemical changes as in rickets. Although it has been stated that the blood calcium is high, Miles and Feng found a marked reduction of blood calcium, a negative calcium and a positive phosphorus balance. There is no more proof for halisteresis in this disease than in rickets, since the loss of calcium from the bones might well be explained by a normal catabolism of bone with an inadequate anabolism. The studies of Korenchevsky and of Miles and Feng point toward the fundamental identity of rickets and osteomalacia.

Scurvy.—Scurvy, or Möller-Barlow disease, is a general disease which attacks infants and children more commonly than adults. Its manifestations are found especially in multiple small hemorrhages and in lesions of the bones. It is due to a dietary deficiency of the so-called water soluble C vitamine, a thermolabile substance found in fresh milk, fruits, especially the orange, and certain vegetables, particularly the potato. Although the subjects usually have secondary anemia, particularly of a severe chlorotic type, the hemorrhages are apparently due to an increased permeability of capillary walls, demonstrated by the "capillary resistance test" rather than by finding histological lesions in the vessels. The small hemorrhages occur in subcutaneous tissue, dentulous gums, and sometimes in the internal viscera, the alimentary canal and frequently under the periosteum of the bones. There is a striking disposition to edema of the skin and certain of the serous cavities; the process in the latter may become exudative in character and lead to adhesions. Rapid heart rate is often observed and at autopsy many cases show hypertrophy of the heart particularly on the right side. The various features of scurvy are admirably discussed by Hess.

In infants and children the bones show striking changes. The costochondral junctions are enlarged so as to resemble closely the rachitic rosary, but in many instances the enlargements are angular and irregular. Similar enlargement may be palpated at the ends of the bones of the extremities, but as a rule the pathological alteration is more striking in the ribs than in other bones. The lesion involves the junction of diaphysis and cartilage and grossly appears as a curved, transverse, pale yellow bar, the convexity of the curve being toward the bone. Histologically, this is a field of disorganization in which fragmented

trabeculae of spongy bone, recent or old hemorrhage and detritus lie in a confused mass. The number of osteoblasts is reduced. The proliferating columns of cartilage cells are somewhat irregularly arranged and toward the center of the bone are reduced in number. The intervening bony trabeculae are irregular in shape and size. The marrow is more fibrous and less vascular than normal. In the human marrow the bony trabeculae are usually poorly calcified, but in animals, although very slender, they are well calcified. The corticalis is thin and often the seat of osteoporosis. There is frequently a disjunction of the diaphysis and epiphysis, and sometimes the epiphysis is displaced into the poorly calcified diaphyseal end. Fractures of the shaft are not uncommon and are followed by the production of large amounts of callus. Hemorrhage into the periosteum is associated with edema, subsequently organizes and becomes calcified.

In adults the bony lesions are not so severe and the anemia, edema and hemorrhages are prominent. The hemorrhage of the gums only occurs when teeth are present and appears in the connective tissue immediately under the mucosa. In an experimental analysis of the disease Wolbach and Howe conclude that it is characterized by an "inability of the supporting tissues to produce and maintain intercellular substances."

Inflammations.—Inflammations of bone usually begin either in the periosteum or in the marrow. Periostitis may be confined to the periosteum and not involve the bone. Osteomyelitis, or inflammation of the marrow usually involves the bone. The term osteitis is usually restricted to those cases where spongy bone is involved without extension to the marrow cavity of the shaft. Inflammation of any of these origins may extend so as to involve marrow, bone and periosteum and is then called panosteitis.

Acute Periostitis.—Simple periostitis occurs in children and poorly nourished adults as a result of direct trauma or without known cause. The periosteum is swollen, soft and tender. Histologically, there are hyperemia, marked edema and infiltration of a few leucocytes. It may heal, sometimes with the formation of small masses of bone, osteophytes, or may progress to more severe forms. It is usually abacterial, but may occasionally contain organisms of low virulence, especially *staphylococcus aureus*.

Purulent periostitis may be due to infected wounds, to extension from neighboring infections, may be hematogenous or may be secondary to acute infectious diseases. It usually begins in the deeper layers as an exudative inflammation, which rapidly results in the accumulation of pus between the bone and the outer layers of the periosteum. In the more favorable cases the bone is not involved, and the abscess points through the soft tissues and skin with discharge of the contents, and cure. In other cases, the pus may remain and become inspissated to form a cheesy mass, which is finally organized. In less favorable cases the inflammation involves the soft parts, with extensive suppuration, or leads to necrosis of bone and involvement of the marrow.

Occasionally acute purulent periostitis becomes transformed to a so-called albuminous periostitis or *periostitis albuminosa*. This is probably due to a

reduction of virulence of the bacteria or an incomplete development of resistance of the host. The lesion may also be primary. It runs a subacute or chronic course, and shows in the deeper layers of the periosteum a viscid cloudy fluid which is rich in albumin and contains fibrin, degenerated cells and a few leucocytes; rarely it contains mucoid.

Acute Osteomyelitis and Osteitis.—Acute purulent osteomyelitis is most common in early life, affects in order of frequency the femur, tibia, humerus, and is unusual in other bones. It begins usually in the spongy diaphyseal end. Rarely the process may be confined to the epiphysis. In the large majority of cases it is hematogenous in origin and is secondary to pyemia or other acute infectious disease. In a few cases it appears to be primary but is probably secondary to some hidden focus of infection elsewhere. It may be caused by infected wounds, by compound fractures, or result from direct extension from neighboring inflammations. The organisms most commonly found are the pyogenic staphylococci and streptococci, but bacillus typhosus, pneumococcus

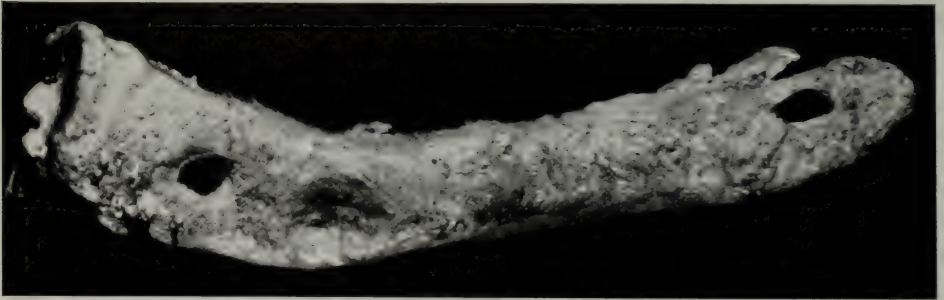


FIG. 387—Chronic suppurative osteomyelitis of tibia with two sinuses. Hamann Museum.

and other bacteria are occasionally recovered. In the spongy bone or marrow there is a diffuse exudative inflammation with focalized abscesses which tend to become confluent. The process extends into the denser bone through the Haversian system and may involve periosteum, may extend to diaphyseal cartilage, sometimes with diaphyso-epiphyseal separation, to the epiphysis and to the joint.

Sequestrum Formation.—Especially in osteomyelitis, but also in periostitis, necrosis of the bone occurs. This is not necessarily coordinate in extent with the severity of the lesion. Although it may be due to direct destruction of the bone by the inflammation, yet it is probable that the inflammatory thrombosis of nutrient vessels is the most important cause (Lewis). The dead bone becomes separated from the living tissue to form a sequestrum. Sequestra may be made up of central part of the bone, central sequestra, or the peripheral parts, cortical sequestra, or of the entire thickness, total sequestra. Granulation tissue or the inflammatory process may lead to partial or complete destruction of sequestra. New bone may partially or completely encapsulate a sequestrum and constitutes the so-called involucrum. The dead bone may be identified by its white color when washed free of blood, or, histologically, by its entire lack of cellular elements (see Phemister).

Course and Sequels.—Acute osteomyelitis may have a short or a very prolonged course. It may rapidly or slowly lead to a general septicemia or pyemia. It may be complicated by more or less distant foci in other bones, which are sometimes almost symptomless (silent foci of Phemister). It may regress and remain quiescent, only to become active as the result of accidental



FIG. 388—Chronic suppurative osteomyelitis of humerus with sequestrum formation. Hamann Museum.

or surgical trauma, or local loss of resistance. When it heals, restitution of bone occurs, or there may be residual areas of dense or porous bone.

Chronic fibrous periostitis may occur as a result of acute simple periostitis or accompany chronic lesions of bone or neighboring soft tissues. The periosteum is thick, dense, fibrous and adherent to the bone. It is often difficult to distinguish this lesion from a cicatrization of an acute process.

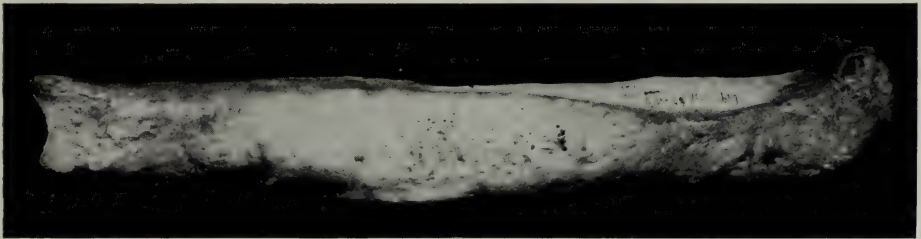


FIG. 389—Chronic ossifying periostitis of the tibia. Hamann Museum.

Chronic Ossifying Periostitis.—This differs from the fibrous form in the deposition of new bone. Similarly, it occurs in connection with chronic inflammations and tumors of bone, chronic inflammations of neighboring soft parts, around fractures and areas of necrosis, may occur in rickets and syphilis, and may rarely be primary. The new bone is formed in the deep layers of the periosteum, is of porous spongy character, with the main trabeculae vertical to the bone surface, and is sometimes covered with compact bone. The nodules or osteophytes may be single, or multiple over a large area. Small osteophytes may be absorbed. The larger areas may fuse with the underlying bone to constitute a hyperostosis. Occasionally in late pregnancy and the puerperium,

presumably as the result of altered calcium metabolism, the so-called puerperal osteophytes may form in the cerebral dura mater.

Chronic Osteomyelitis and Osteitis.—Under a variety of conditions, including prolonged acute osteomyelitis, tumors, fractures, tuberculosis, syphilis, necrosis and other lesions, chronic inflammation occurs which may lead to absorption of bone, rarefying osteitis, which is an inflammatory osteoporosis, or to condensation of the bone, condensing or ossifying osteitis. Both may be combined.

Rarefying osteitis is essentially a formation of granulation tissue from the marrow, and a consequent absorption of bone either as lacunar resorption by enlargement of the Haversian system, or by the formation of perforating canals as described in discussing osteoporosis. The process is of importance in providing for the separation of sequestra.

Caries is a local manifestation of essentially the same process, which leads to a complete breaking down of the bone. It may proceed from the outside as peripheral caries or from the inside as central caries. The soft necrotic bone is usually moist because of exudation of fluid and leucocytes from the granulation tissue, and true pus formation may occur. Less commonly exudation is absent and the lesion is spoken of as dry caries or *caries sicca*.

Condensing Osteitis.—This proceeds in the outer layers of the marrow and in the Haversian system. The marrow becomes dense and fibrous (chronic fibrous osteomyelitis) and new spongy bone is formed which gradually increases in density. Preëxisting spongy bone becomes more and more compact. The original compact bone increases in density due to deposition of bone in the Haversian system. The bone may become extremely dense and of ivory-like hardness, the so-called eburnation of bone. The disease is not common but is seen most often in males under thirty years of age (see Henderson).

The term osteosclerosis is often regarded as synonymous with condensing osteitis but osteosclerosis may present essentially the same changes without any clear sign of inflammation, as for example, in akromegaly. Condensing osteitis is usually limited to one or a few bones, but an osteosclerosis may be widely distributed as for example in cases of leucemia or anemia, associated with marked thickening of bone and reduction of marrow, a combined bone-blood disease (see Oesterlin). M. B. Schmidt regards the bone change in these cases as secondary to the marrow lesion of the blood disease and perhaps cicatricial in nature.

Chronic Sclerosing Non-suppurative Osteomyelitis.—This lesion, sometimes called Garré's disease, is usually observed in the lower extremity and presents a fusiform, firm swelling of the shafts of the bone, with reduction in the size of the marrow cavity and a thickened but only slightly adherent periosteum. The cortical bone is eburnated. The marrow may show considerable fibrosis. In some cases there may be necrosis of part of the bone with the formation of a sequestrum. The lesion probably originates in some preceding general infectious disease (see Henderson).

Osteitis Deformans (Paget). Osteitis Fibrosa (von Recklinghausen).—These two diseases differ but slightly and are probably fundamentally of the same nature. The process is essentially a resorption of bone associated with the formation of much osteoid tissue, which shows little or no tendency to calcification. The resorption is by lacunar resorption and perhaps also by the formation of perforating canals; there is serious doubt that halisteresis plays any part. Osteitis deformans or Paget's disease is uncommon and occurs principally in the aged. It affects especially the tibiae and flat bones of the skull, but other bones, notably the vertebrae, are likely to be involved. The bones gradually become thick and soft and the long bones show curving. Collapse of the soft vertebrae produces shortening of the trunk. Generalized osteitis (or more properly osteomyelitis) fibrosa occurs in earlier life, also shows resorption of bone, but with less osteoid than in Paget's disease and instead a progressive fibrosis of the outer layers of the marrow. The distribution may be much the same, but femora are more often attacked than tibiae and the skull is less markedly involved. The marrow fibrosis may take on the character of

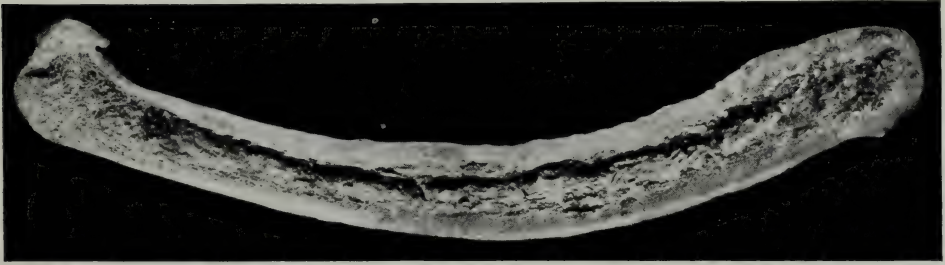


FIG. 390—Osteitis deformans of femur. Hamann Museum.

fibroma or of fibrosarcoma. Sometimes masses of pigmented giant cells closely resemble benign giant cell epulis or sarcoma, but in many instances probably represent the encapsulation and organization of hemorrhages. Both diseases may show cyst formation but this is more common in osteitis fibrosa. Although osteitis fibrosa is a disease of adult life, it may occur in young individuals, more especially, however, in localized rather than generalized form. The local affection of one or of a few bones is rare. The bony deformities and the reduction of cranial capacity may lead to serious nervous lesions. Leontiasis ossea is different in distribution and, as has been indicated, probably periosteal in origin.

The cause of the condition is unknown. Vague infections and also syphilis have been discussed but no proof of their relationship offered. Osteitis fibrosa suggests neoplasm, but this phase is probably a result rather than the cause of the condition. The disease is not confined to man and may affect many other species (see Christeller).

Infectious Granulomata. Tuberculosis.—Tuberculosis is usually hematogenous, but occasionally may be due to direct extension from neighboring areas, as for example tuberculous lymph nodes. In generalized miliary tuberculosis, small tubercles are often found in the marrow and sometimes in the periosteum, but the bone remains unaffected.

Tuberculous periostitis not uncommonly involves ribs and bones of the face. It may be due to direct extension or may be blood borne. The lesion begins in the deeper layers of the periosteum, becomes caseous and may extend widely along the long bones. The underlying bone may show tuberculous caries.

Tuberculosis of the bone may begin as a tuberculous osteitis or tuberculous osteomyelitis. It is common in childhood and early life but also occurs in adults. In childhood about one-third of the cases are due to bovine bacilli (Girdlestone), whereas in adults practically all are due to the human variety. It is said that tuberculosis may be primary in bones but this may be an error,

due to difficulty in finding a lesion in a portal of entry. In childhood the bone lesion is often secondary to lymph node tuberculosis and in adults to pulmonary tuberculosis (MacKinnon). The disease tends to attack spongy bone such as vertebræ, ends of long bones, short bones of hand and foot, skull and pelvis. This is probably because of the rich vascularization with greater likelihood of lodgment of bacilli (see Nussbaum, Kolodny). Trauma often occupies a prominent place in the history. Recent opinion (see Sénequè) based on experimental and clinical observation is to the effect that if trauma has any significance, it is in the awakening of a latent process rather than in establishing a point of lowered resistance for the lodgment of organisms.



FIG. 391.—Healed tuberculosis of fourth and fifth lumbar vertebræ, with partial destruction and a marked kyphoscoliosis of the spinal column. Hamann Museum.

and destroys it. The destruction is usually in the form of a tuberculous rarefying osteitis, but there may also be condensing osteitis. There is little disposition to new bone formation. At times, granulation tissue, with few bacilli and few tubercles, predominates, shows little caseation and is called granulating or fungous tuberculosis. The destruction of bone is limited and the process may continue for a long time with little or no deformity. It may, however, become caseous or the process may be caseous from the onset. Caseous osteomyelitis may produce extensive destruction of bone with sequestrum formation, or sequestration may be due to extensive vascular obstruction by the lesion in the marrow. In contrast to the sequestra of acute osteomyelitis, those of caseous tuberculosis are the seat of rarefaction and are often carious. Secondary infection, with suppuration, may be carried

Tuberculous osteomyelitis begins as a small tuberculous mass which gradually enlarges, involves the bone

in by the blood stream, or enter through fistulæ. As the disease penetrates through the bone, it involves the soft parts to produce caseous tuberculosis (cold abscess) which proceeds directly to the surface or along fasciæ, as for example, from tuberculous Pott's disease of the vertebræ along the psoas fascias to the groin or buttock.

Syphilis.—In congenital syphilis the usual lesion of the bones is osteochondritis syphilitica. Longitudinal section of the long bones of the newly born congenital syphilitic shows at the diaphyso-epiphyseal junction a more or less broad, irregular, chalky or light yellow zone, instead of the normal straight narrow gray line. Histologically, M. B. Schmidt distinguished two forms. The one appears to be principally an abnormality of development with a broad zone between diaphysis and epiphysis, in which there is a network of broad bands of calcified cartilage containing marrow. The other, more truly inflam-

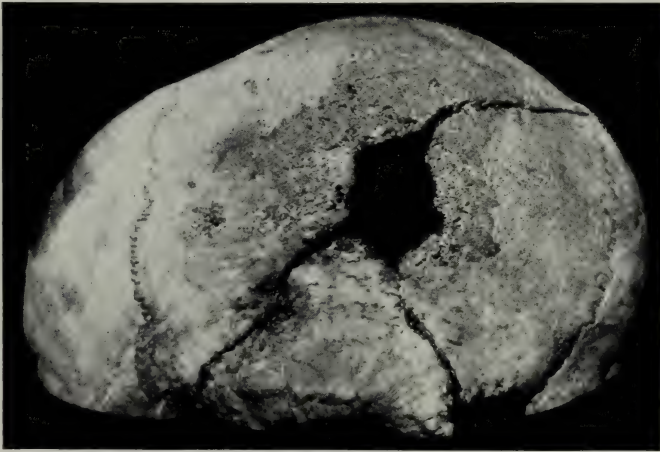


FIG. 392—Syphilitic caries of skull. From collection of Dr. Dudley P. Allen.

matory, shows in addition to the calcified cartilage, a mass of granulation tissue derived probably from the perichondrial tissue, which projects irregularly into the cartilage. The fragile calcified cartilage permits epiphyseal separation upon slight trauma. *Treponema pallidum* is present in variable numbers (see review of entire subject by Schneider). Much less common is the progressive ossifying periostitis. Rarely the periosteum shows gumma formation.

The bone lesions of acquired secondary syphilis are found in the periosteum in the form of localized or fairly extensive swellings. The periosteum is the seat of hyperemia, slight edema and infiltration of cells, especially small mononuclears. In later stages of the disease there may be an ossifying chronic periostitis, especially likely to affect the anterior tibial borders and the vertex of the skull. The osteophytes fuse to form more or less extensive hyperostosis, often associated with a similar process in the endosteum and extensive endostosis. Gumma occurs in the periosteum and usually causes destruction of the underlying bone, sometimes with extension into the marrow.

Gummatous osteomyelitis begins either in the marrow or spongy bone as

circumscribed, usually multiple nodules, with the characteristic gross and microscopic features of gumma. The enlargement of the lesions causes destruction of bone and formation of sequestra. Whereas in tuberculosis new bone formation is uncommon, in syphilis it occurs in the immediate neighborhood of the lesion, often with the production of overlying osteophytes and hyperostosis.

Syphilitic caries is especially likely to occur in the flat bones of the skull. It apparently begins as a gummatous periostitis which extends widely into the tables, more particularly as perforating canals, and produces a worm eaten appearance. It is usually a caries sicca with the formation of large, fragile and spongy sequestra, which remain under the intact fascias and skin. The neighboring bone shows condensing osteitis and the margins are elevated by production of new bone. The destruction is usually confined to the external and superficial part of the middle tables, but may extend through the entire thickness of the skull.

Falling of the bridge of the nose, "saddle nose," is due to destruction of the



FIG. 393.—Fractures considered in relation to the character and line of fracture: (a) longitudinal fracture; (b) transverse; (c) oblique; (d) spiral; (e) subperiosteal; (f) V-, T-, or Y-shaped; (g) compression; (h) comminuted; (i) impacted; and (j) crushing.

bones of the septum and bridge, but the gummatous process usually starts in the mucosa and involves the bone secondarily.

Actinomycosis, owing to its common situation near bones, as for example the jaw, involves the neighboring bone in a superficial rarefying osteitis and peripheral caries, with underlying granulation tissue.

Leprosy of bones begins as osteomyelitis with the cellular make up of the lepra nodule, which leads gradually to partial or complete resorption of the affected bone without necrosis or sequestrum formation. It is possible that leprous neuritis produces a trophic atrophy, either with or without leprous osteomyelitis. The loss of distal phalanges in anesthetic leprosy is due to repeated unsensed trauma and secondary infection with resultant local osteomyelitis.

Fractures and Their Repair.—Fractures, interruptions of continuity of bone or cartilage, may be due to direct violence or to muscular contraction. They are most frequent in the second, third and fourth decades of life and much more common in males than females. Among other predisposing causes, destructive disease of bones is conspicuous, particularly tumors, osteomyelitis, erosion by aneurysms, and such diseases as osteomalacia, osteogenesis imperfecta, etc. Fractures may be partial, in the form of fissures and

“green stick” fractures of young bones, or complete when the fracture involves the entire thickness. Closed fractures do not communicate with body surfaces; compound fractures show either penetration of bony fragments upon surfaces or are due to injuries, such as gunshot wounds, in which the surface is injured at the same time as the bone. In relation to the line or lines of break, fractures may be longitudinal, tranverse, oblique, spiral, V, T, or Y shaped, or comminuted. Compact shaft may be pushed into the spongy bone at the end to produce impacted fractures. Subperiosteal fractures occur without rupture of periosteum. There may or may not be displacement of the fragments.

The injury results in hemorrhage in the immediate neighborhood, with hyperemia and often edema. Repair is influenced by a variety of factors such as age, apposition and immobility of fragments, infection, lesions of nerves, alterations of general metabolism, especially of calcium and phosphorus, endosteal and periosteal blood supply, diet (Watanabe) and perhaps disturb-



FIG. 394—Faulty union of multiple fractures of tibia and fibula, with malposition and excess bone formation. Hamann Museum.

ances of glands of internal secretion (Kolodny). Under favorable conditions the course of events is as follows. The endosteum and periosteum provide granulation tissue, which grows around the point of fracture, to form externally a spindle-shaped mass. This becomes fibrous; osteoid and cartilaginous tissue are formed in irregular masses, and the whole constitutes callus. Blood vessels penetrate from the fractured ends, as the cartilage and osteoid become truly ossified. By the action of osteoblasts and osteoclasts a regeneration is effected and the enlargement reduced nearly, or sometimes quite, to normal size. Usually, the compact bone which ultimately remains is somewhat thicker than normal. Under less favorable circumstances, the ossification remains throughout most of the original extent of the callus, the union may be much delayed, or there may be no union, the bone ends simply held together by fibrous tissue to form a mobile “false joint.” Infection may delay union or, if the resultant osteomyelitis be severe and extensive, may produce such great destruction as to prevent union. Albanese refers to the regeneration of the bone as an anatomical repair; when the new bony structure has adapted itself to meet any new lines of stress, functional repair has occurred.

Tumors.—Primary tumors of bone may arise from periosteum, endosteum, perhaps from bone cells, and from marrow. With the exception of marrow tumors and certain others, many of the benign and malignant tumors tend to produce bone or cartilage in the course of their growth. The classification of the Registry of Bone Tumors of the American College of Surgeons (Codman) places all the benign tumors which form bone or cartilage, such as osteoma, chondroma, fibro-osteoma and combinations of these, under the general heading of osteochondroma. The fibroma and myxoma, not clearly of osseous origin, and the angiomas are not included in this group. The giant cell tumor of the epulis type is regarded as benign. The malignant tumors which produce bone are included under the general heading osteogenic sarcoma. The other malignant tumors of importance are the endothelioma and the myeloma. This classification will be followed in a general way, but it is important to note that in a tissue with such great possibilities of abnormal cell proliferation as is bone, confusion of diagnosis is readily possible.

Fibroma is much more frequently periosteal (peripheral) than endosteal (central) in origin and, although uncommon, affects the bones of the face more often than other bones. Fibromas may grow in the bony air sacs and are sometimes found in the tooth sockets or jaw as fibrous epulis. They may calcify, ossify, or become cystic. They should not be confused with old granulation tissue.

Myxoma, as a pure tumor, is rare and arises in periosteum more often than in endosteum. Usually the tumor is a myxochondroma. In either case there is a decided tendency to recur after removal. Bloodgood regards the myxoma as a sarcoma.

Angioma, originating from either blood or lymph vessels, is rare, usually central and shows telangiectases.

Osteochondroma in this classification includes osteoma and chondroma, neither of which is likely to occur in pure form, and various combinations of these with each other and with fibrous and mucoid tissue. The combination may be so complex as to be spoken of as fibro-osteomyxochondroma or may show fewer elements.

Osteoma.—The principal members of this group are the exostoses and enostoses. It is difficult and often impossible to distinguish these tumor forms from the osteophytes of inflammatory origin. The exostoses and enostoses grow from bone and may be spongy, medullary if they contain marrow, compact or eburnated. Two subvarieties are discussed by Schmidt as cartilaginous and fibrous exostoses, both of which are likely to be multiple. The cartilaginous exostoses begin in the cartilaginous part of the diaphyso-epiphyseal junction, show bone centrally and cartilage peripherally, extend down the metaphysis and shaft as the bone grows and cease to grow when the bone is mature. The fibrous exostoses originate in periosteum, tendons or fascias. The periosteal forms are seen most often on the flat bones of the skull; the tendinous and fascial forms represent excessive growth of normal tuberosities and bony crests.

Chondroma.—This may be single or multiple and usually appears in the interior of the bone as enchondroma. Eecondroma is rare. The enchondroma affects the phalanges of the hand and may be bilateral. Less often it occurs in the foot, the pelvis, the scapula and other bones of endochondral type of growth. The tumor presumably originates in remnants of growth cartilage. The histological examination shows irregularity in arrangement and often of size of the cells and lacunæ. The intercellular tissue may be osteoid in character, producing the osteoid chondroma. Bone formation, producing the osteochondroma, is frequent. The tumor, even though neither histologically nor grossly malignant, shows a striking tendency to recur after removal. This is true also of the more complex tumors. The sacrococcygeal chordoma, discussed in the chapter on tumors, closely resembles a cellular chondroma and is believed by many to be of this nature.

Giant Cell Tumor.—This is also called giant cell sarcoma and benign giant cell sarcoma. It occurs especially in the ends of long bones as a soft, friable, dark red mass, which destroys the spongy bone. It may extend to and destroy compact bone, but penetration is delayed by new bone formation in the periosteum. With rare exceptions it does not penetrate the soft tissues and does not metastasize. Histologically, it is made up of round cells or spindle cells, is well vascularized and contains numerous large multinucleated giant cells. Mallory regards these

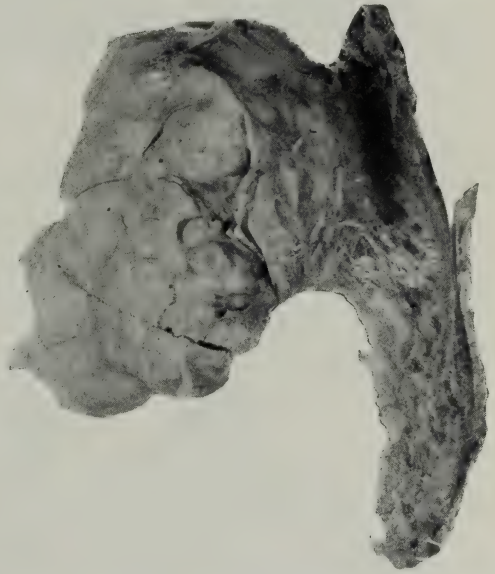


FIG. 395.—Osteoma of scapula, the result of foreign body irritation. Army Medical Museum, 17875.

cells as foreign body giant cells, and appears to regard the lesion in certain instances as inflammatory rather than neoplastic. The condition should not be confused with malignant tumors in which fusion or multiple mitosis leads to the formation of a moderate number of multinucleated cells. The giant cell tumor is also common in the jaw, as a giant cell epulis, where it is probably identical with that in the long bones, but usually is paler, firmer and much less vascular.

Sarcoma.—With the exception that he includes the benign giant cell tumor in this category for convenience, Ewing classifies the bone sarcomas as the osteogenic sarcoma, which may be fibrocellular, telangiectatic, or sclerosing, the myeloma and the endothelioma.

Osteogenic Sarcoma.—The cells of the osteogenic sarcomas are principally spindle cells, variable in size and outline and often so short and rounded as to look like round cells. Ewing, however, maintains that round cells arise only

from the marrow. The nuclei show great variability in chromatin arrangement and content. The intercellular substance varies much in amount, may be fibrous or hyaline, osteoid or osseous. The vascular supply is also variable in amount, almost always sarcomatous in character with close apposition of tumor cells, and the vessels not infrequently contain tumor thrombi. The more

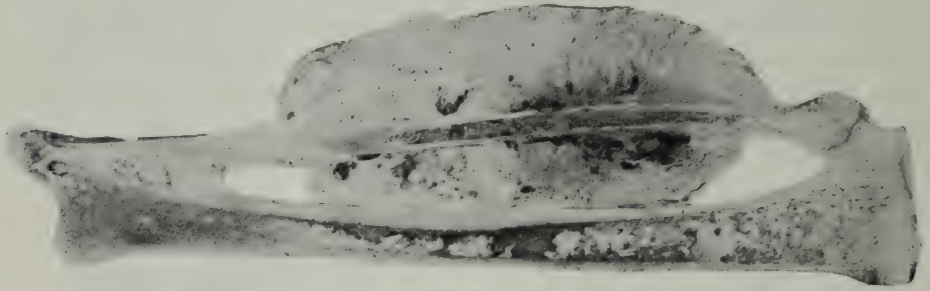


FIG. 396—Osteogenic sarcoma of fibula and tibia, periosteal in origin. Army Medical Museum, 17872.

cellular, rapidly growing tumors are likely to invade the neighboring soft parts, and to metastasize early and widely by way of the blood stream.

The fibrocellular osteogenic sarcoma is best exemplified by the periosteal spindle cell sarcoma. This originates in the deeper layers of the membrane, attacks long bones, especially of the extremities, and nearly always develops

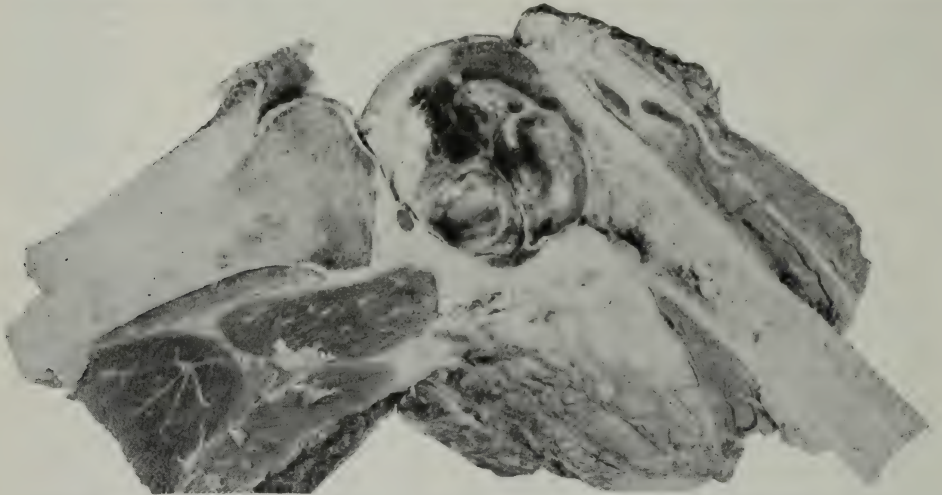


FIG. 397—Osteogenic sarcoma of the lower end of the femur, telangiectatic in type. Army Medical Museum, 17904.

near the ends of the shaft. Its growth is often rapid, extends around the shaft as a dense spindle formed enlargement and, while it may not penetrate into the bone, often does so with the formation of a smaller mass within the spongy bone or marrow cavity. Bone formation is usually moderate in amount, as spongy masses, but may be extensive and lead to a bony hardness of the entire tumor. Lines of bone formation radiate out from the shaft. Whilst usually a large spindle cell tumor, the cells may be small and rounded or large and polyhedral.

The larger polyhedral cell tumors may show much cartilage with little bone or may be almost entirely devoid of both.

The telangiectatic sarcoma may arise in any part of the bone, but is somewhat more often central than peripheral. It invades so rapidly as a rule, that the periosteum does not form a new layer of bone. Histologically, the cells are usually rounded or polyhedral, lacking uniformity in size, and many of the nuclei are hyperchromatic. It is characterized by the presence of many large vascular spaces, from which hemorrhage is not infrequent. Foreign body giant cells may be so numerous as to suggest benign giant cell sarcoma, but the vascularization and the types of tumor cell are usually sufficiently characteristic.

The sclerosing osteogenic sarcoma is not common but is central more often than peripheral. It is characterized by slow growth and the formation of new bone in the tumor, which may become extremely dense. It invades pre-existing bone, the shaft of which may be much enlarged, to form a solid spindle

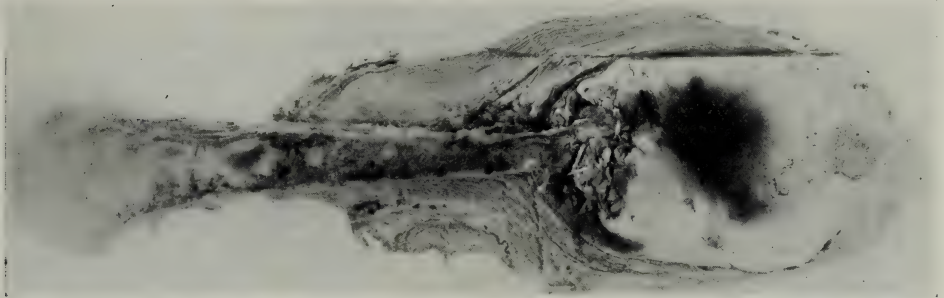


FIG. 398—Multiple myeloma of humerus, which at one end has become invasive. Army Medical Museum, 17871.

form swelling. The cellular parts show the usual arrangement of sarcoma. In spite of the slow growth, metastasis is frequent.

Bone Aneurysms.—In discussing the bone sarcomas, mention of the so-called aneurysms of bone is necessary. These are usually situated near the ends of long bones, are more or less invasive, often pulsate and sometimes a bruit is audible. Ewing expresses the view that most of these are telangiectatic sarcomas, in which the vessels are extremely large and the cellular content much reduced in amount. Others may be due to softening of a giant cell tumor so that blood flows directly through the large central space. They are not aneurysms in the strict sense of the word.

Myeloma has been discussed in the chapter on tumors. The tumor is almost always multicentric in origin and is derived from the marrow of ribs, sternum, skull and other bones. There is usually an associated Bence-Jones albumosuria. The tumor invades the bone and may extend into the soft parts. Metastases to the viscera are not rare. New tumors in other bones are probably a manifestation of system disease rather than metastases. The tumors are soft, gray, poorly defined, poor in reticulum, well vascularized and may be made up of plasma cells, of large lymphoid cells or of cells which closely resemble those of the marrow. They do not form bone.

Endothelioma.—Much of our knowledge of this tumor of bone is due to the studies of Ewing. The tumors usually affect only one bone but may be found in several bones (see Kolodny). They are richly cellular, well vascularized, invade the bone and soft parts but do not metastasize readily. They are not osteogenic. They may be accompanied by severe anemia. They are readily susceptible to treatment by x-ray but are not permanently cured and recur. There are three principal forms. The solitary cystic telangiectatic angio-endothelioma affects the ends of long bones as a large, invasive, highly vascular mass which sometimes has the character of bone aneurysm. The multiple endothelioma affects a large number of bones, especially spongy bone, as small tumor nodules. The solitary diffuse endothelioma occurs in the shaft of a long bone with absorption of the bone and thickening of the organ as a whole. Other bones may be involved subsequently, and metastasis to the viscera is not uncommon. Histologically, the telangiectatic form shows a



FIG. 399.—Pathological fracture of femur due to osteogenic sarcoma of the shaft.

pseudo-alveolar arrangement of large polyhedral cells with loosely arranged cytoplasm and relatively small nuclei. The tumor is richly vascularized and shows wide, cavernous blood spaces. The multiple endothelioma shows cells of the same type, arranged in sheets, sometimes multinucleated, but the large vascular spaces are infrequent or absent. These tumors often resemble cancer metastases. The solitary, diffuse form shows broad sheets of cells similar to those in the other forms, but usually smaller, and the picture may suggest lymphosarcoma.

Secondary Tumors.—Carcinomas of prostate and breast frequently show metastases to spongy bones such as vertebræ, ribs, pelvis, ends of long bones and other situations. They may be nodular or diffuse. They may be osteoclastic or osteoplastic. The latter are more or less destructive but show also new bone formation in the neighborhood, in the tumor itself and in the periosteum. Thyroid carcinomas commonly metastasize to bone, but usually as discrete masses in bones in and near the neck such as clavicle, sternum and upper ribs. Bone metastases from carcinomas in other situations are by no

means rare. Sarcomas also metastasize to bones either as central discrete nodules or as flattened masses in the periosteum, and are usually osteoclastic.

Cysts.—Cysts of the bones may be monolocular or multilocular. They may result from the breakdown of benign or malignant tumors, or from hemorrhages, and are common in osteitis fibrosa, where, according to Bloodgood, they occur principally in the shafts of long bones. Cysts of the jaw have been discussed in the chapter on alimentary canal.

Parasites.—Echinococcus cyst of the bones affects spongy bones especially, and produces atrophy of bone by pressure. Sequestra may result from necrosis due to involvement of blood supply. Penetration of the bone leads to thickening of the periosteum and hyperostosis. Fractures may result from destruction of the bone. Cysticercus cellulosa is rare in man but more frequent in lower animals (Rievel).

JOINTS

Congenital Anomalies.—The most important of these is congenital dislocation of the hip. This occurs much more frequently in females than males and in about one third the cases is bilateral. It is due in most cases to a hypoplasia of the acetabulum, so that the socket is flattened, associated with which the head of the femur is often of somewhat conical shape. In contrast to traumatic dislocations, the joint capsule and ligaments are not ruptured, but are stretched and thickened. The head of the femur is displaced upward toward the dorsum ilii, usually posterior, sometimes anterior. Malposition of extremities in utero may lead to partial dislocation of joints. Traumatic dislocations may occur during labor.

Legg's disease, Perthes' disease, Calve's disease, is a lesion of the epiphysis of the head of the femur in children, much more common in boys than girls. The ossification proceeds irregularly and in Phemister's case there was turbid fluid, villous synovial membrane and necrosis of the epiphysis. Clinically, it may be confused with tuberculosis (see Allison and Moody, Phemister).

Koehler's disease is a condition in which the tarsal navicular bone is of abnormal shape, size and density. It occurs in children, more often boys than girls (see McClure).

Osgood-Schlatter disease occurs in childhood and adolescence and affects boys more often than girls. It is a painful lesion of the tubercle of the upper tibial epiphysis as it extends downward anteriorly, usually associated with separation of the tubercle (see Osgood).

Various hypotheses have been advanced as to the cause of Legg's, Koehler's and the Osgood-Schlatter affections. Valentin regards them as due primarily to congenital developmental anomaly of the epiphysis, which remains quiescent until the period of active exercise. Trauma is only an occasional factor of importance.

Circulatory Disturbances.—Hemorrhage is usually due to injury. The blood may remain fluid for a long time and apparently may be completely absorbed. If clots form, they undergo organization, sometimes with slight fibrous adhesion of joint surfaces. In either event the synovial membrane is

likely to show hemosiderin pigmentation. Pigmentation of this membrane also occurs in hemochromatosis and in hemorrhagic diseases.

Joint Lesions in Hemorrhagic Diseases.—Especially in hemophilia but also in other hemorrhagic diseases, particularly Schoenlein's disease, lesions of the joints may occur, which should not be confused with infectious or rheumatic joint affections. Hemorrhage into the cartilage and joint may be followed by fibrosis and pigmentation of the synovial membrane, as well as some calcification. The cartilage may show degeneration and erosion as far as the bone (see Freund, also Rosenfield).

Acute Inflammations.—Acute arthritis may be primary or secondary, monarticular or polyarticular. Primary arthritis may be due to trauma, especially penetrating injuries. Kaufmann includes also those forms in which, even although the infectious agent be blood borne, the lesion is found especially in the joints with minor or no lesion at the portal of entry, as for example, rheumatic fever. Secondary arthritis may be due to direct extension of inflammation from the neighboring bone or soft parts, or may be hematogenous.

The hematogenous forms occur in infectious diseases, notably in pyemia, but also in many other diseases such as typhoid fever, erysipelas and the acute exanthemata, pneumococcus infections and gonorrhea. These are often spoken of as metastatic arthritides, and in certain diseases such as typhoid, erysipelas, pneumococcus and gonococcus infections the organisms can be recovered from the joints, but in the exanthemata of unknown origin it is difficult to say whether the joint lesions are truly metastatic, or are due to poisonous products of the disease.

Acute serous arthritis is usually monarticular, may be due to trauma, to infection, or may occur without known cause. The inflammation affects mainly the synovial membrane and shows hyperemia, edema and serous exudation into the joint cavity. The disease either heals or may become chronic with fibrosis of the membrane. If bacterial in origin it may progress to suppuration.

Acute serofibrinous arthritis is usually of bacterial origin, the organisms gaining entrance either by direct infection or by blood transport. It is usually polyarticular and is the form seen in rheumatic fever. The inflammation is confined to the synovial membrane, but the surrounding parts may be the seat of hyperemia and edema. The membrane is covered with a thin film of fibrin, and flocculi are present in the fluid. The cavity is filled and somewhat distended with cloudy limpid fluid, which contains in addition to the fibrin a moderate number of leucocytes and mononuclear cells. The lesion may heal completely or there may be slight residual fibrous adhesion.

Acute suppurative arthritis is due principally to direct extension from neighboring foci of suppuration, when it is usually monarticular, or due to blood transport, as in pyemia or other infectious disease, when it may be either monarticular or polyarticular. The pus in the cavity may be small in amount or may be mixed with serum to fill the sac. Usually the inflammation involves the periarticular structures and is especially serious because of destruction of

cartilage. As a result the bone may be involved in a suppurative osteitis. If the cartilage be spared, the lesion may heal with contraction of the capsule and fibrous adhesion of joint surfaces (false ankylosis). If the bone be laid bare and the lesion heal, the apposed bony surfaces organize and ossify to form a permanent union (true or bony ankylosis). The destruction of cartilage is greatest at the points of closest contact between the articular surfaces (Phemister).

Rheumatic fever is to be regarded as a systemic disease with special manifestations in joints, heart and other organs (see Swift). Cold and moisture seem to be important predisposing causes, and the disease has a certain familial incidence (Faulkner and White). Although usually acute, its course may be prolonged. Although certain organisms, as the diplococcus of Poynton and Paine and the streptococcus viridans (see Clawson), have been described as the exciting cause, transmission experiments have been generally unsuccessful (Miller) and the postulates of Koch not met. Its association with tonsilitis and with chorea have not been explained. Clinically, it is a febrile disease with swelling, redness, pain and tenderness in certain joints, with a tendency for migration to new locations as the older ones clear up. Pathologically, the joint lesion is a fibrinoseous inflammation, often with extremely little fibrin, which involves principally the synovial membrane. The periarticular structures show hyperemia, edema and slight cellular infiltration. Fahr describes granulomatous nodules in the synovia and periarticular structures somewhat resembling Aschoff nodules of the myocardium, which he suggests are latent foci from which recurrences of the disease may arise.

Gonococcal arthritis is often spoken of as gonorrheal rheumatism, but is in reality a metastatic involvement of the joint from genital gonococcal infections of long standing and deep situation. It may complicate other gonococcal infection such as that of the conjunctiva (DiBella). It is usually monarticular, affecting the knee joint, but may appear in other joints and may be polyarticular. It begins in acute form but may persist for a long period with less severe symptoms. Pathologically, it may be a serofibrinous arthritis, or it may be a purulent arthritis with suppurative involvement of the periarticular structures. Gonococci may be recovered in pure culture from the exudate.

Chronic Arthritis.—This term includes a variety of chronic lesions of the joints, difficult of classification because of combinations of lesions. The involvements of synovial membrane, of cartilage, of bone and of joint capsule are usually sufficiently distinctive to permit of a fair degree of differentiation. Included as a chronic arthritis is the dry ulcerative form, which has little or no inflammatory reaction. Arthritis deformans constitutes the great group of chronic non-tuberculous inflammations of the joints.

Chronic dry ulcerative arthritis occurs in the aged and is usually monarticular with involvement of the hip joint, but may affect knee, shoulder, elbow or fingers. The lesion is probably of nutritional origin and is principally degeneration, atrophy and fibrosis of the cartilage. The ulceration is usually

superficial but may lay bare the bone; reaction in cartilage or bone is slight or absent. The synovial membrane may become thickened and fibrous.

Arthritis Deformans.—For the sake of convenience this will be classified in two forms. The first form, which has the descriptive name chronic adhesive arthritis, is considered by many to be different in nature from the second form,



FIG. 400—Arthritis deformans of spinal column, showing lipping of the joint borders and bony bridges between adjacent vertebral bodies. Hamann Museum.

osteo-arthritis, which shows more extensive bony involvement. Chronic adhesive arthritis is therefore considered as a topic separate from arthritis deformans by numerous authors, especially those of the German school. Nichols and Richardson, as well as others, regard them as somewhat different manifestations of the same underlying nature, and their conception is adopted here. These authors classify the two lesions as proliferative and degenerative. Others, as Goldthwaite, classify them as atrophic and hypertrophic. Fisher quite rationally offers the terms synovial and chondro-osseus. We employ the terms chronic adhesive arthritis and osteo-arthritis because they have wider usage.

Chronic adhesive arthritis, the proliferative type of Nichols and Richardson, the synovial type of Fisher, is also spoken of as rheumatoid arthritis or chronic rheumatism. It is a progressive disease, often polyarticular in distribution. The lesion begins in the synovial membrane, usually at the margins of the cartilage, as a growth of vascularized connective tissue, granular in type, which gradually extends over the articular surface. With the thickened synovial surface, or articular pannus, the deeper connective tissues of

the synovia and of the perichondrium are involved. This may result simply in fibrous adhesions between the joint surfaces, made more serious if the capsule be fibrosed, but frequently the underlying cartilage disintegrates and the bone may be irregularly denuded of cartilage and covered only by the granulation, or denser fibrous, tissue. The connective tissue of the marrow proliferates in the form of granulations and there follows a new formation of osteoid, and then of bony trabeculae. Bony union between the joint surfaces, bony ankylosis,

may be brought about by ossification of fibrous adhesions, or by ossification of proliferating cartilage, or by endosteal bone formation in the epiphyses. In some cases synovial tags, like those of osteo-arthritis, are formed. Subluxations are not uncommon and ankylosis may fix the joints in abnormal position.

Osteo-arthritis, the degenerative form of Nichols and Richardson, the chondro-osseous form of Fisher, the great second type of Ely, is regarded by many as the lesion included in the term arthritis deformans, or chronic deforming arthritis. The primary change is in the cartilage, usually in the center, as a fibrillation associated with softening of the hyaline matrix and a disappear-



FIG. 401—A resected knee from a typical case of arthritis deformans. Tibia on the left, condyles of the femur on the right. From Ely, *Inflammation in Bones and Joints*.

ance of the fibrous part of the perichondrium. Many of the cartilage cells disappear, but others show multiplication. The erosion of the cartilage is irregularly distributed and the opposite articular surface may show proliferation of cartilage or bone. Thus, the cross section of the joint surfaces may be markedly irregular. This may produce interlocking with limitation of motion, but no true ankylosis is likely to occur. Larger areas of bone end may be denuded with a resultant condensing osteitis. The motion of the joint may produce a highly polished porcelain-like appearance to the bone ends. There is also a bony proliferation which produces the so-called lipping of the joint, an irregular marginal projection of bone. This is probably due to a proliferation of perichondrium at its junction with capsule, which ossifies, and the proc-

ess may be contributed to by periosteal bone formation from the margin of the epiphysis. It should not be confused with slight lipping that is common in persons of more than thirty-five years of age, without joint lesions (Willis). The synovial membrane and the capsule may be markedly fibrosed. From the synovial membrane, especially at the joint margins, numerous sessile or pedunculated masses of connective tissue may grow, in villous arrangement. These may be of vascularized connective tissue or edematous fibrous tissue. The tissue may differentiate to form cartilage, bone or fat, "lipoma arborescens." The little masses may break loose from their peduncles and appear free in the cavity as "joint mice." Small tumor-like masses of cartilage or bone,

the capsular enchondroma or osteoma, may form within the capsule and may also give rise to joint mice.



FIG. 402—Chronic infective arthritis of the knee. The central parts of the cartilage are eroded and the peripheral parts preserved.

Chronic infective arthritis may be monarticular, but is usually polyarticular, and may involve spine, wrists, knees, ankles, tarsal joints and finger joints. It appears to be associated with foci of infection as for example in the tonsils, the alveolar processes and the deeper genitalia. Pathologically, it is the milder form of synovial chronic arthritis, often with villus formation, but may become more severe. Its tendency is toward recovery, especially after removal of the focus of infection, in contrast to the progressive character of both forms of arthritis deformans.

Similar lesions have been produced

experimentally by the injection of streptococci, staphylococci and pneumococci (Nathan).

The cause of arthritis deformans is unknown. The proliferative or adhesive form is sometimes associated with trauma or various infectious diseases, and osteo-arthritis may have the same history or be associated with dislocations, bone tumors, diseases of the central nervous system. Osteo-arthritis is more commonly a disease of advanced life. Metabolism has been studied by Pemberton, by Cecil, Barr and DuBois and others, without demonstrating any constant abnormality. Pemberton's studies indicate the possibility that a decreased blood flow, with decreased oxygen saturation of the tissues, may play an important part in depressing the nutrition of the bones and joints.

Still's Disease is a chronic polyarthritis in children, probably of infectious origin, with synovial hyperplasia, with peripheral involvement of the carti-

lage, thinning and perforation of the central parts of the cartilage, and rarefaction of the bone.

Infectious Granulomata. Tuberculosis.—As with bones, tuberculosis may affect the joints at any period of life, but is especially common in childhood. In childhood, bovine bacilli are most commonly the cause (Frazer). Most cases are secondary to obvious tuberculosis elsewhere, due to hematogenous transport, but so-called primary tuberculous arthritis occurs with no demonstrable primary lesion in another site. Nichols expresses the view that the bacilli always lodge first in the bone marrow, although most agree (Ely) that the lesion may originate either in the marrow or in the synovial membrane. Experimentally, Frazer found the synovial membrane more susceptible than the bone marrow. As with bones, trauma probably excites a preëxistent lesion instead of furnishing a point of diminished resistance. Whitman states that the spine is most frequently affected, and next in order the hip, knee, and tarsus, elbow, wrist, and shoulder.

Primary synovial involvement, less common pathologically than the primary diaphyseal form, affects usually the knee. The membrane is the seat of an acute or subacute inflammation, shows numerous small tubercles, and the cavity becomes filled with a fibrin-ous exudate. As a rule, the periarticular structures, the cartilage and the bone are not involved.

Beginning in the marrow of the diaphysis, rather than in the epiphysis, tuberculosis extends to the joint and invades along the capsule and the margins of the cartilages. Phemister points out that in contrast to pyogenic infections, the articulating surfaces of the cartilages may remain free for a long time. Indeed the lesion may remain in capsule and periarticular tissues as a tuberculous granulation tissue, producing "white swelling," for a considerable period before the joint is invaded. Involvement of the joint is usually in the form of a fungous arthritis. Tuberculous granulation tissue grows from capsule and synovia and destroys cartilages, especially at the margins. The cavity contains a cloudy, thick, semipurulent fluid which contains leucocytes, fibrin, desquamated fatty degenerated cells from synovial membrane and tubercles,

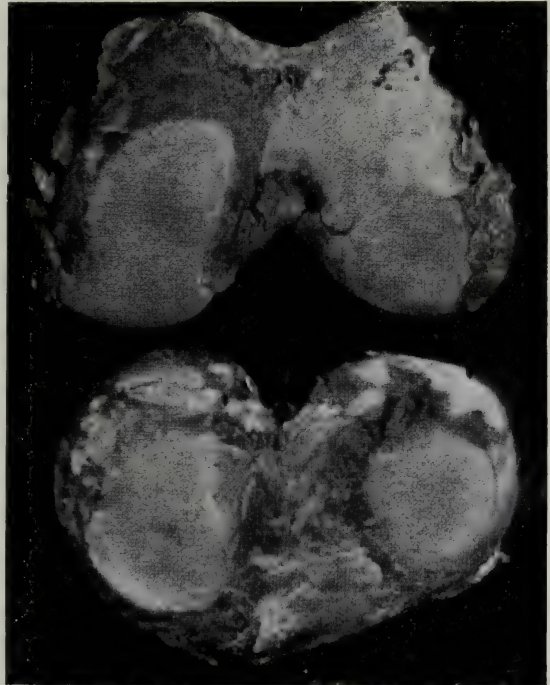


FIG. 403.—Tuberculosis of knee. Cartilage preserved where patella and tuberosities come in contact with femur, and partly destroyed along unopposed surfaces of tibia and femur. From Phemister, D.B., *Annals of Surgery*.

and a relatively small number of bacilli. The formation of villi, like those of osteo-arthritis may be extensive. In severe cases, the granulation tissue may destroy all or nearly all the cartilage by growth over the surface as pannus, or extension between cartilage and bone. This is followed by tuberculous caries of the bone end. Tuberculosis does not ordinarily stimulate new bone formation, and therefore ankylosis does not occur.

Frequently the exudate of tuberculous arthritis contains the so-called *rice bodies*, small, flat or oval, pale yellow, firm masses a few millimeters in diameter. They are made up of fibrosed or hyaline fibrin, or may be derived from small masses of granulation tissue broken off by the joint movements.

Syphilis.—In congenital syphilis and in early acquired syphilis, joint manifestations occur, but little is known of their exact nature. In late acquired syphilis gummatous involvement of the joint may be secondary to lesions in the synovial membrane or the bone end. The cartilage may be destroyed and the joint be extremely nodular. The synovial membrane may become markedly fibrosed and adherent.

Leprosy may be accompanied by a joint lesion like osteo-arthritis, or in the anesthetic form may exhibit neuropathic arthropathy.

Coccidioidal granuloma occurs in bones and joints, in characteristic form, and may be confused clinically with tuberculosis (Ely).

Special Lesions. Gout.—Although many lesions of joints are suspected of being metabolic in origin, this conception is unqualifiedly applicable to gouty arthritis. It may be monarticular or polyarticular and is especially prone to occur in the metatarsophalangeal articulation of the great toe, and also in fingers and hand. The lesion may be entirely periarticular, or may involve capsule, synovia, cartilage and bone. Wells accepts the view that the urates, especially sodium urate, are primarily deposited, if rapidly, with acute inflammation, especially hyperemia and edema, if slowly, with little or no reaction. Necrosis occurs secondarily in the area of deposition. The destruction of cartilage may be merely an ulceration with fibrillation of the hyaline matrix, or adhesion with fibrous ankylosis may result.

Neuropathic Arthropathies.—More especially in tabes dorsalis and syringomyelia, but also in other organic nervous diseases, central or peripheral (Phillips and Rosenbeck), the joints may be involved. This is usually monarticular in larger joints such as knee, hip, shoulder or elbow. The onset is usually abrupt with a considerable exudation of fluid into the joint. It may for a time closely resemble osteo-arthritis, but is different clinically in that it is painless. It usually progresses to, or may be primarily, the destructive lesion of joint structures and bone referred to as Charcot's joint. The destruction involves synovia, cartilage and often a considerable extent of bone, leaving a large joint cavity filled with clear or slightly cloudy fluid. With the destruction of articular surface and bone, the capsule becomes fibrosed, the joint becomes flail-like and subject to subluxations and dislocations. In some cases there is in addition to the destruction, a proliferation of cartilage and bone to

form irregular, projecting masses in the joint, which may become free bodies. Often there occurs marked lipping, sometimes with bony and cartilaginous masses in the capsule and periarticular structures.

The direct cause is not known, but it is possible that the ill-controlled ataxic gait of tabes may throw strains upon the knee joint that excite the changes. In some cases trauma seems to play a part (Heyman).

Loose Bodies.—These have been referred to above as joint mice. According to Ely three classes are recognized, those which result from intra-articular fracture, those due to disease, especially osteo-arthritis, and those of uncertain



FIG. 404.—Neuropathic arthropathy (Charcot joint) of knee.

origin spoken of as “essential joint mice.” As to whether this last group is caused by loss of nutrition and sloughing (osteochondritis dissecans of Koenig), to embolism of bacteria or fat, or to fracture has not been finally established. Phemister states that after detachment, degenerative and proliferative processes take place, in that the original cartilage and bone undergo gradual necrosis, and there is a subsequent proliferation of fibrocartilage which becomes calcified or ossified.

Tumors.—Lipoma, fibroma and various types of sarcoma occasionally occur. Secondary tumors may invade the joints from metastases, or from primary growths in the adjacent bone or soft parts.

SKELETAL MUSCLE

Rigor mortis has been discussed in the chapter on death and necrosis.

Congenital Anomalies.—These represent complete or partial defects in the development of muscles or groups of muscles. The condition affects especially the muscles of the shoulder girdle, although others may be involved. The chief manifestation in addition to the obvious deficiency of muscle is elevation of the scapula. Small remaining bundles of muscle are histologically normal. The condition is probably due to fault of embryonal development of the muscle, since examination of the spinal cord shows no lesion that can be held responsible (see Busse).

Retrogressive Changes.—Cloudy swelling and fatty degeneration have much the same characters as in cardiac muscle. In the former, the muscle substance is granular and shows diminution or loss of transverse striation.

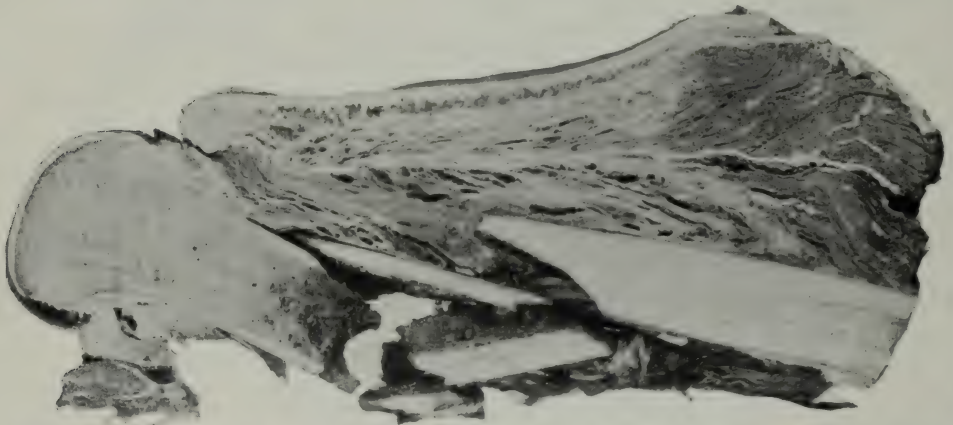


FIG. 405—Gas gangrene of muscles and compound comminuted fracture of femur due to shell wound. Army Medical Museum, 2879.

In the latter there are, in addition, fat globules in longitudinal rows, which soon occupy the entire width of the fiber. These conditions occur as the result of infectious diseases, inflammation in the muscle and intoxications, especially by phosphorus and poisonous fungi. Fat infiltration occurs sometimes as a replacement process consequent upon atrophy. Hyaline necrosis, waxy degeneration or Zenker's hyalin, has been described in the chapter on degenerations and infiltrations. It affects especially the recti abdominis, but may be seen in other muscles, as the result of infectious diseases, notably typhoid fever and influenza. Grossly, the muscle is pallid, glassy and fish-like, and often shows hemorrhage. Microscopically, the fibers lose transverse and longitudinal striations, become structureless, often show fracture and retraction within the sarcolemma. Subsequently, there may be infiltration of large and small mononuclear cells and proliferation of sarcolemma nuclei. Since the sarcolemma is not destroyed, regeneration may occur.

Necrosis due to direct injury or vascular occlusion may show hyaline or granular necrosis, or both, of the muscle fibers. The reaction otherwise is the

same as in other tissues. *Gas gangrene*, due to invasion of saprophytic anaërobres, especially *bacillus aërogenes capsulatus* of Welsh, has been discussed in the chapter on death and necrosis. The muscle is at first pallid and fish-like, loses its contractility, is usually foul smelling, and subsequently becomes dark brown in color and finally filled with gas bubbles. Microscopically, the muscle necrosis is usually granular and the large bacilli numerous and easily recognizable.

Circulatory Disturbances.—Passive hyperemia occurs as the result of general or local disturbances. Hemorrhage occurs as the result of wounds and in the course of acute infectious diseases, hemorrhagic diseases and intoxications. Unless the collateral circulation is much reduced, as for example by arteriosclerosis, small emboli do not produce infarction. The occlusion of large vessels, whose terminals show little anastomosis, by ligation, thrombosis, embolism, and the reduction of large areas of circulation by tight bandages, lead to granular necrosis with resultant partial or complete loss of function.

Atrophy may be widespread, due to general exhausting diseases such as chronic tuberculosis and malignant tumors, and due to the deteriorative changes of senility. The local forms include the atrophy of inactivity, due to suppression of function such as occurs in ankylosis of joints, and neurotrophic atrophy. The latter is really an inactivity atrophy when the lesion is in the central neuron, and is not so

severe as when the peripheral neuron is affected. Peripheral lesions such as nerve section and neuritis, imply not only inactivity but also a trophic influence, which latter seems to be manifested only in extra-uterine life (see Jamin).

Grossly, atrophic muscle may be soft or firm, normal or dark brown in color or pallid, and reduced in bulk. Microscopically, the fibers are reduced in transverse diameter but with clear transverse striations, and may finally disappear. There may, however, be a few hypertrophic fibers (Durante, Schmidtman). The sarcolemma nuclei increase in number and may fuse. Sometimes brown granules of pigment are found in considerable quantities. These represent iron-bearing and non-iron-bearing derivatives of the muscle pigment myoglobin, a pigment not identical with hemoglobin (Günther). The muscle may also show cloudy swelling and the condition is referred to as degenerative atrophy, a term not justified in the light of our present knowledge of the degenerative nature of atrophy in general (see Bradley). The bulk of the muscle may be

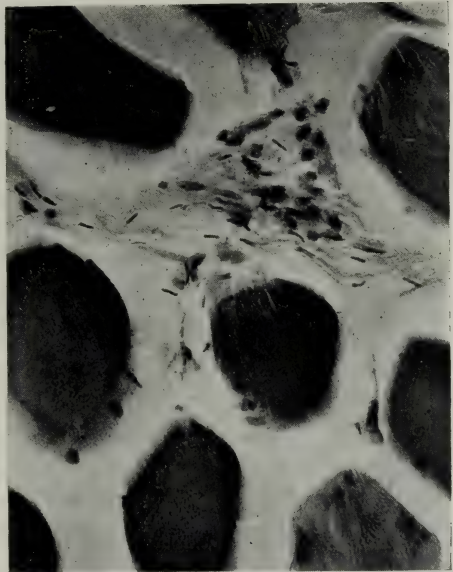


FIG. 406.—Muscle, the seat of gas gangrene, stained by MacCallum's method for bacteria. Army Medical Museum, 31044.

fairly well retained or even increased by an infiltration of fat. Chen, Meek and Bradley find that the loss of weight follows a logarithmic curve, tending to reach an equilibrium; that there is no increase in water content, greater amounts of amino-acids are liberated in postmortem autolysis than by normal muscle, due probably to conversion of structural proteins into digestible forms during atrophy, and that the hydrogen ion concentration is essentially normal.

Special Forms of Atrophy.—The muscle atrophy of progressive spinal muscular atrophy, type Duchenne-Aran, belongs in the group of neurotrophic atrophy, since the peripheral neuron shows an associated atrophy.

Juvenile progressive muscular atrophy of Erb or progressive pseudohypertrophic muscular dystrophy, which is familial and occurs usually in early life, is in part an atrophy and in part a hypertrophy. It is independent of nerve involvement and is to be regarded as a dystrophy of the muscle itself (see Myers). Not only is there atrophy of many fibers, but many others show marked hypertrophy, and numerous fibers are vacuolated. Fat infiltration of the perimysium is frequent. Gibson, Martin and Buell state that there is a decreased ability to transform creatin, a decreased output of creatinin and a creatinuria, and sometimes hypoglycemia and deficient glycogenesis.

In many forms of muscular atrophy, the perimysium is fibrosed and may become so infiltrated with fat, that grossly the muscle is of normal size or somewhat enlarged, the so-called pseudohypertrophy.

Myasthenia gravis is included here for convenience, even although atrophy of the muscles is not constant. It occurs at almost any period of life but is most frequent in the third decade, and affects the sexes about equally. The muscles are readily fatigued and a long time is necessary for their recovery. Ultimately they may be practically paralyzed. In a few cases persistent or hyperplastic thymus has been found, but this is not sufficiently frequent to qualify the disease as of thymic origin and its cause remains unknown. The muscle may be of normal size or somewhat reduced in bulk and is likely to be flabby. Microscopically, the fibers may be normal or the seat of cloudy swelling or hyaline necrosis; the sarcolemma nuclei may multiply. Occasionally atrophy is observed. Most characteristic is the presence of focal collections of lymphoid cells, so-called lymphorrhages, near which the muscle changes may be pronounced. Lymphorrhages may be present in heart and other viscera. Except for the observation of lymphorrhages in spinal ganglia the nervous system shows no important lesions. There is no alteration of creatinin balance but blood sugar may be reduced and glucose tolerance diminished (Gibson, Martin, and Buell).

Hypertrophy is due to increased work, as for example, that of the blacksmith and athlete. The increase in bulk and weight is due to an increase in the transverse diameters of preëxistent fibers and is not a multiplication or hyperplasia.

Myotonia congenita is a familial disease, almost certainly hereditary and transmitted as a Mendelian dominant (Rosett, Nissen). It begins in early life as an enlargement of several or many groups of muscles, not strong in proportion to their size, easily fatigued, responding well to reflex and electrical

stimulation, but relaxing slowly, and exhibiting a peculiar electrical curve. There is no lesion of the spinal cord. Microscopically, there is an increase in the transverse diameters of most of the fibers and an increase in the number of nuclei. Heidenhain describes in the outer part of the sarcoplasm, transversely arranged fibrils that encircle the fiber in ring or spiral fashion. Some fibers are definitely atrophic. Myotonia atrophicans shows the same tonus as myotonia congenita, may subsequently disappear, may occur later in life as an acquired disease, affects especially muscles of the face and shoulder, and microscopically shows predominantly atrophic fibers.

Regeneration of skeletal muscle, aside from the usual factors controlling regeneration, depends upon the extent of the injury and the degree of involvement of the perimysium. A clean wound with little destruction may be followed by practically complete regeneration. The sarcoplasm forms processes, or muscle buds which usually contain numerous nuclei. The buds from the adjacent fibers meet, fuse and form longitudinal fibrils with transverse striations, while the nuclei decrease in number and assume the natural lateral position. If destruction be extensive, the muscle buds cannot bridge the gap, and the area is filled with scar tissue. If only the contractile substance be injured, as for example, in Zenker's hyalin, the dead muscle is removed by phagocytosis and the defect filled by regeneration of the sarcoplasm.

Acute myositis may be suppurative or non-suppurative. The suppurative form may be due to direct extension from neighboring abscess or from superficial ulcers. Pyemia does not frequently produce muscle abscesses, perhaps because of relatively decreased circulation while the muscles are at rest. Pyemic abscesses are usually small, elongated collections of pus, but if the condition continue they may attain a diameter of a centimeter or more. Abscess of muscle may complicate typhoid fever and be due either to the bacillus typhosus or to pyogenic cocci (see Busse). Rarely suppuration may occur without a determinable portal of entry. Microscopically, the pus is made up in part of leucocytes and in part of tissue cells and muscle. The muscle nuclei in the neighborhood show multiplication, principally amitotic, and increase in chromatin content.

Non-suppurative inflammations are rare. *Acute polymyositis* may follow acute infectious diseases or may apparently be primary. It involves many muscles in the form of localized painful swellings, runs a febrile course of a few weeks and may lead either to complete recovery, sometimes with residual atrophy, or to death, especially when respiratory muscles are involved. The skin over the involved areas may show an urticaria and the disease is accordingly sometimes called dermatomyositis. Microscopically, there are edema, slight fibrin formation, infiltration of lymphoid cells and sometimes small areas of hemorrhage. The muscle substance shows cloudy swelling and vacuolization. Pyogenic cocci have been isolated (Busse). *Acute crepitating perimyositis* is also extremely rare, and is due to a fibrinous edema of the perimysium and the inner surfaces of the muscle fascias. Rarely a polymyositis may be associated with output of dark brown urine which contains myoglobin,

myositis myoglobinurica (Gunther). The reaction to *trichinella spiralis* will be discussed with parasites of the muscles.

Chronic Fibrous Myositis.—In this lesion there is a productive overgrowth of connective tissue between the muscle fibers, which varies from a young cellular type to the older fibrillar or even hyaline form. Atrophy of the muscle may accompany the lesion, in which case it is often difficult to say that the fibrosis is inflammatory, because it may be a replacement fibrosis subsequent to atrophy. Fibrosis of the sternocleidomastoid muscle is found in congenital wry neck or caput obstipum. There is question in these cases as to whether the fibrosis is inflammatory, or a cicatrization following rupture during labor, or fibrosis secondary to some fault in intra-uterine growth of the muscle.

Myositis Ossificans.—Although it is not clearly demonstrated that the lesions are inflammatory, two forms of myositis ossificans are distinguished, a local form and myositis ossificans progressiva multiplex. Local ossification may follow traumatic injury or hematoma of muscle (Kidner), and occurs in the adductors of the thighs as "rider's bone" and in the shoulders of soldiers as the result of repeated trauma in rifle drill. Injury of muscle may be followed by granulation, cicatrization and ossification, with or without the intermediation of cartilage formation. In some instances it is due to periosteal fragments in the injured area, but in others it seems to be truly metaplastic. In rider's bone and similar conditions the bony spur may or may not be connected with the bone at the tendon insertion. This lesion is probably subsequent to the fibrosis which follows repeated fine tears in the muscle during exercise.

Progressive multiple ossifying myositis is a disease which begins in early life, affects boys more often than girls and ends in death after a course of one or two decades. Numerous muscles are affected, with painful swellings, edema of the overlying skin, and evanescent fever. Ossification ensues and progressively increases, but finally may lead to reduced function and atrophy, and may extend from one bone to another so as to immobilize the joint, usually in a position of flexion. The lesion is primary in the aponeuroses, tendons, sometimes the ligaments, especially those of the spinal column, and may extend from the periosteum. From these regions the fibrosis and ossification extend into the connective tissues of the muscles. Microscopically, the muscle fibers lose their cross striations, undergo complete atrophy and are replaced by the growing connective tissue. Ossification proceeds from the connective tissue or may follow cartilage deposition. Various hypotheses have been offered as to the cause of the disease, but, as Opie points out, it is probably a progressive anomaly of osteogenesis. This supposition is based on the early age of incidence, the rarefaction of skeletal bone as revealed by the x-ray, and various associated anomalies, especially microdactylism of the great toes, from which one phalanx may be missing.

Tuberculosis.—The most common form of tuberculosis of the muscle is conglomerate tuberculosis, or tuberculous abscess, due either to direct extension or lymphatic transmission from some neighboring focus such as bones, joints, or lymph nodes. Muscles are rarely involved in a generalized miliary

tuberculosis. The reason for the infrequency of miliary tuberculosis is unexplained, for it may be produced experimentally with apparently little difficulty (Saltykow). The tubercles are made up from the connective tissues; the muscle cells play no part in their formation.

Syphilis.—The characteristic lesion is the gumma, which may attain great size. Multiple small gummata may also occur. In addition, skeletal muscle may show a chronic interstitial inflammation with consequent fibrosis and atrophy of the muscle fibers, similar to that observed in the myocardium in syphilis (Busse).

Tumors.—Tumors of skeletal muscle are not common. Most of them arise from supporting tissues rather than the muscle fibers. The hemangioma may be cavernous or capillary, may attain considerable size and may be locally invasive. Fibroma and myxoma are uncommon. Lipoma may penetrate between muscle bundles. Primary sarcoma is also infrequent. Rhabdomyoma is rare, if indeed it ever occur, in skeletal muscle. Metastatic tumors do not often involve skeletal muscle.

In addition to the usual manifestations of low grade inflammatory reaction around tumors, the muscle may show atrophy. Furthermore, there may be a marked proliferation of the muscle nuclei.

Parasites.—Aside from the occasional occurrence of echinococcus cysts and other cysticerci, the most important parasite of muscles is the trichinella spiralis. This nematode is introduced into man usually by ingestion of infested pork, which is not cooked sufficiently to kill the parasite. The encapsulated larvæ are liberated in the duodenum and mature in about forty-eight hours. Nausea, diarrhoea and fever may occur about twenty-four hours after ingestion, probably because of absorption of poisonous products released by digestion of the cyst wall of the larvæ. Sexual reproduction occurs and the females, in two or three weeks give birth viviparously to embryos, which gain access to the blood stream and are deposited within the sarcolemma sheaths, where they assume a coil form and are encysted by connective tissue. The involvement of the muscles may be almost symptomless or may produce fever, and pain, stiffness and swelling of the muscle. Microscopically, practically all the larvæ are in the same stage of encystment. By the study of experimental trichinosis of the rabbit, Ehrhardt has found that in the first few weeks there is hyperemia and a rich migration of leucocytes. This is followed by swelling and proliferation of the sarcolemma which results in fibrous encystment. In the meantime the involved muscle fibers have undergone cloudy swelling, fatty degeneration and necrosis. The neighboring fibers may show hydropic or fatty degeneration or hyaline necrosis. Attempts at regeneration may be observed as minute muscle buds, but more especially in multiplication of the muscle nuclei principally by mitosis. Human muscle may show minute white or gray, firm specks, which histologically are found to be the coiled larvæ. In some cases inflammation may still be present, and in others the encystment may be complete with little or no remaining reaction other than the cyst wall. Ultimately, the parasite dies and may become calcified.

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CHAPTER XXII

THE NERVOUS SYSTEM

CONGENITAL ANOMALIES.
CONGENITAL AND FAMILIAL DISEASES.
RETROGRESSIVE CHANGES.
REACTIONS OF INTERSTITIAL TISSUES.
TRAUMATIC INJURIES.
CIRCULATORY DISTURBANCES.
INFLAMMATIONS.
GRANULOMATA.
INFECTIOUS DISEASES.
DISEASES OF OBSCURE ORIGIN.
TUMORS.

Introduction.—It must be recognized that the subject of neuropathology is so extensive that the material in a general text book can be representative of only the most important lesions. Furthermore, the disturbances of function are in many instances so intricate that their correlation with alterations of structure can only be indicated in the briefest fashion. The various parts of the nervous system, the meninges, brain, spinal cord, peripheral nerves and sympathetic system are so closely interrelated in pathological changes, that a consideration of each part separately may readily lead to much duplication and perhaps an incorrect conception of the various special diseases. The mode of presentation which is adopted for this chapter is based upon the works of Buzzard and Greenfield and of Ernst.

Congenital Anomalies.—These are most frequently due to defective closure of the neural groove. Anencephaly, with complete absence of the brain including cerebrum and cerebellum, is accompanied by absence of the flat bones of the skull and rudimentary basal bones. Hemicephaly is a less marked degree of the same anomaly, in which rudimentary basal ganglia and cerebellum are found and the skull defect, hemicrania, is less severe. Moderate or slight defects in the skull may be accompanied by a bulging of brain substance, exencephaly, or merely of the meninges, meningocele.

Spina bifida, or rachischisis, exhibits lesions varying in severity from those which are incompatible with life to those which give no symptoms whatever. In complete or total spina bifida, usually associated with anencephaly, the vertebral processes are incomplete, the posterior part of the cord does not fuse and the incompleated central canal lies exposed or covered only by meninges and skin. Incomplete or partial spina bifida occurs usually in the lumbosacral region as a defect of bony and muscular development. The medullary groove is closed but the cord may be rudimentary. Overlying the meninges in the defective area is a pad of fat. Usually there is an outpouching of meninges and cord which constitutes meningomyelocele. Much less common is an outpouching of meninges alone, meningocele. In spina bifida occulta, there is no outpouching and the only indication of the defect in the spine is an area of hypertrichosis localized to that region (see Cutler).

Other developmental defects occur with a completely formed bony case. *Microcephaly* is a hypoplasia of the cerebrum, associated with abnormal thickness of the skull and early closure of sutures and fontanelles. The cerebrum may be of adult or embryonal type, or resemble that of lower animals, but the cerebellum is usually well developed. Occasionally, as in amaurotic familial idiocy, there may be partial or complete agenesis of the cortex, often associated with other anomalies of brain development. *Microgyria* is a condition in which the gyri are small and the sulci shallow. It is usually associated with other anomalies such as microcephaly. A pseudomicrogyria may be produced by fetal inflammations of meninges and cortex. *Cyclencephaly* is a failure of separation, or fusion, of the cerebral hemispheres, which is usually associated with cyclopia. In *porencephaly* there is a failure of development of cortical white and gray matter, so that the ventricles communicate with the surface of the brain. The cavities are lined by a continuation of the pia-arachnoid. If



FIG. 407—Infant with spina bifida. Army Medical Museum, 30896.

bilateral, the lesions are usually symmetrical and may be so severe that there is almost no cortex, but even in these cases the basal ganglia persist. There may also be dystrophy and agenesis in remote parts of the brain, in the cord and pons (LeCount and Semerak). Pseudoporencephaly may be the result of cyst formation following destructive lesions of the brain, but in these instances, the cavity is lined by a cicatricial thick wall, and remnants of the original lesion, especially blood pigment and compound granule or scavenger cells, may be found.

Rarely cells may be found in abnormal positions, a sort of heterotopic misplacement, as in the case reported by Babonneix.

Tuberous sclerosis is a condition in which more or less numerous nodules occur in various parts of the brain. These are rounded or elongated, usually well defined, pallid, and vary in diameter from a few millimeters to several centimeters. Microscopically, glia fibrils are present in large numbers. In addition to smaller glia cells there are large round cells, some of which are ganglion cells and others of which are not to be positively identified, but are probably glia matrix cells of higher differentiation than spongioblasts (Biel-

schowsky). An atrophic form is described in which there are numerous small cavities surrounded by fibrillar gliosis. Tuberous sclerosis is sometimes accompanied by tumor-like or tumorous lesions elsewhere, as congenital tumors of the kidney, rhabdomyoma of the heart and adenomatous proliferations of the cutaneous sebaceous glands. The nature of tuberous sclerosis is not yet clearly defined. It is apparently a disturbance in development of tissue from the primary neural groove cells, perhaps hamartomatous in character. It may possibly lead to the development of glioma. It is discussed here rather than with tumors because it is not clearly proven to be blastomatous.

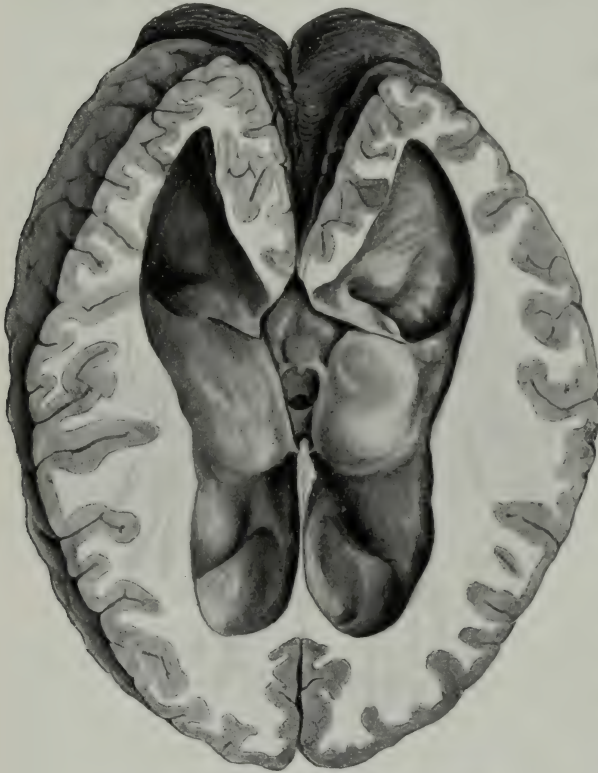


FIG. 408—Acquired internal hydrocephalus.

Hydrocephalus may be congenital or acquired. External hydrocephalus, a distention of the arachnoid space by accumulation of fluid, is usually congenital and of doubtful etiology, but may be acquired by disease of the larger lymph cisterns at the base of the skull (Dandy). Internal hydrocephalus is an accumulation of fluid in the ventricles and is due to occlusion of the outlet of cerebrospinal fluid. The congenital form leads to more severe distention than the acquired form. It may be due to anomalous occlusion of the aqueduct of Sylvius or to occlusion of the foramina of Magendie and Luschka by fetal meningeal inflammations or perhaps to lack

of development of arachnoid villi (Weed). The distention is not usually severe before birth but often progresses markedly after birth. Moderate grades are consistent with normal bodily and mental development, but the more severe progressive forms lead ultimately to death. The pressure has little effect on the basal ganglia but the white matter and subsequently the cortical gray matter, undergo pressure atrophy. As the pressure continues, distention increases, the convolutions become flattened, and finally there may be merely a film of cortical substance, or in places, only meninges, covering the dilated ventricles. The ependyma may be locally or diffusely thickened and adhesions may divide the ventricles into loculi. The head may be enormously enlarged, with open sutures and fontanelles.

Acquired hydrocephalus, considered here for convenience, may be due to meningeal inflammations which close off drainage, to blockage by cysts or tumors, to intracerebral pressure which pushes the pons and inferior parts of the cerebellum into the foramen magnum and thus prevents drainage, and perhaps to certain toxic conditions. The distention leads to enlargement of the ventricles, flattening of the convolutions and pallor of the brain substance, but unless the lesion occur in very early life, the skull is not deformed. If inflammation be still present, the fluid is clouded by exudate, but otherwise the fluid is clear. The ependyma may show inflammation, may be normal or may be hyperplastic as in the congenital form. Rarely a so-called primary hydrocephalus occurs in adults, in which the ventricles are distended with clear fluid, but no cause is manifest (see Weed, also Dandy).

Hydromyelia is a dilatation of the central canal of the cord. In the congenital form the dilatation may be diffuse, is at the expense principally of the gray matter and in cross section has a key-hole or shield outline (Ernst). There may be destruction of the ependyma, gliosis and hemorrhage, and the condition merges into a syringomyelia. Acquired hydromyelia may be due to compression injuries of the cord or to tumors of the cerebellum.

Familial and Congenital Diseases.—In addition to those diseases where muscle involvement is the prominent feature, which have been discussed in the chapter on organs of locomotion, other somewhat similar diseases occur with lesions principally in the nervous system. Some of these attack several members of one generation while others may be traced through two or more generations. Suggestive charts have been made up on the basis of observations and family histories, but it is difficult as yet to say that they exhibit features characteristic of true hereditary transmission (see Crouzon). In some of these it is thought that although the diseases themselves are by no means hereditary, the so-called nervous abiotrophy seems to occur, in which, owing to hereditary or other inherent defect, certain localized regions are unusually susceptible to deterioration (see Vogt, also Jelliffe). Thus, in Friedreich's ataxia certain columns of the cord undergo degeneration without observable cause, and in progressive lenticular degeneration, the lenticular nucleus seems to be susceptible to some vague poison. The pathologic anatomy is given in detail by Klarfeld.

Amaurotic Familial Idiocy.—This disease, improperly called idiocy since it develops after birth, affects several members of a family, but rarely the firstborn, is observed usually in Jews, and as a rule terminates in death before the fourth year of life. The brain is of normal size but the pia-arachnoid fluid is increased in amount, the gyri flat and the sulci wide. The tracts of the cord are small and degenerate, especially the pyramidal tracts. The ganglion cells, especially those of the hippocampus, frontal lobes, gray matter of the cord and to a less extent, those of the cerebellum, show marked retrogression, in the form of swelling, lateral displacement of the nucleus, vacuolization of cytoplasm with increased amounts of lipoids. The Nissl granules are degenerate and clumped about the nucleus. There is often a local balloon-like swelling

of the chief dendrite (Uyematsu). Associated with the nerve lesions, there is at first weakness and flaccid palsy, followed by spasticity and increased reflexes. The eye grounds show a light red fovea centralis and a pale macula, due to atrophy of the fovea and surrounding edema. The retinal cells show degeneration similar to that of the ganglion cells; the optic nerves and ultimately the optic tracts undergo atrophy (see Sachs and Strauss, Hassin).

Friedreich's Ataxia.—This disease begins in childhood or adolescence, often affects several members of the same family, may appear in more than one generation or may show no family relationship. Ataxia begins usually in the lower extremities and progresses upward; muscles of the extremities and trunk are weak but not atrophic, and reflexes depressed or absent; speech may be defective, and there is often nystagmus. Apparently due to the muscular weakness, spinal curvatures and flat foot may occur. Grossly, the principal lesion is of the cord, which is moderately or markedly reduced in diameter. Degeneration accompanied by secondary gliosis is well marked in the posterior columns, more especially the column of Goll, and less marked in the direct cerebellar and crossed pyramidal tracts. The posterior root fibers are degenerate but the ganglion cells show only secondary changes. The cells of Clark's column are reduced in number and atrophic (see Pfeiffer, also Winkelman and Eckel).

Progressive Lenticular Degeneration.—This condition, often called Wilson's disease, is usually familial, occurs during puberty or early adult life and is associated as a rule, but not invariably, with a cirrhosis of the liver. The chief symptoms are intention tremors, progressive muscular spasm followed by contractures, difficulty in speech and a highly emotional state. Grossly, there is degeneration of the lenticular nucleus, varying from numerous small cavities to a single large cavity, symmetrical, affecting chiefly the putamen, to a less extent the globus pallidus and occasionally in slight degree the caudate nucleus and internal capsule. Microscopically, there is degeneration of nerve fibers and cells, together with gliosis which also is subject to degeneration. The lesion is not vascular in origin and is supposed by Wilson to be due to a poison with selective affinity, generated by virtue of the liver lesion. The cirrhosis of the liver is multilobular in character and shows extremely large nodules. The spleen may be enlarged but ascites is rare. In the early stages of the disease icterus may occur but is not a prominent feature of the syndrome (see Hatfield).

Chronic Progressive Chorea.—This disease, often referred to as Huntington's chorea, is familial in incidence, may occur in two generations, begins in middle life and is characterized at first by jerky movements, followed slowly by paralysis and mental deterioration. The pathological changes are somewhat confused, perhaps due, as pointed out by Buzzard and Greenfield, to difficulty in distinguishing in some instances true Huntington's chorea and paretic dementia. There is fibrosis and thickening of the cerebral dura and thickening and adhesion of the pia-arachnoid, sometimes a chronic hemorrhagic pachymeningitis, atrophy, gliosis and increased density of the cortex. Small

areas of softening and of round cell infiltration may be found in the brain substance. The most constant degenerative changes are in the pyramidal cells, especially of the psychomotor areas, with associated tract degenerations and gliosis. Degeneration of ganglion cells occurs also in the corpus striatum, particularly in the putamen and caudate nucleus. For an excellent study of these familial diseases the reader is referred to Orton.

Degenerations.—Essential to the understanding of the degenerations in nerve tissue is the conception of the neuron with its cell and nerve fiber. When a nerve fiber is divided, or its cell body destroyed, degeneration results. Degenerative changes in the cell may be primary, or they may be secondary to lesions of the nerve fiber. Thus, the term degeneration as here employed, covers a variety of changes from minor deterioration to necrosis. When a nerve fiber is divided, the distal part undergoes the so-called Wallerian degeneration. The entire distal part of the axis cylinder becomes fibrillated and exhibits a nodular or varicose swelling. The myelin is converted into droplets of unsaturated fats (Cramer, Feiss and Bullock), positive by Marchi stain, and are further broken down and disappear. The cells of the sheath of Schwann proliferate, phagocytose the destroyed axis and myelin, fill in the defect and extend toward the proximal segment. The changes in the proximal portion are of significance in reference to the regeneration of nerve. Although the myelin degenerates up to the first or second node of Ranvier, the axis cylinder remains intact. In a few hours the terminal part forms a bulb-like swelling and fibrillates in an intricate fashion, and numerous fibrils grow out in all directions. These again may produce bulbs which resemble the pseudopodia of the embryonal nerve cell as described by Harrison. Together with this change the cells of the sheath of Schwann multiply and accompany the growing fibrils. If the distance to be transversed be not too great, or the intervening granulation or connective tissue not too dense, a certain number of the fibrils grow into the original fiber path beyond the injury, and the proliferating sheath cells from both cut ends meet. The sheath cells become arranged in tubular fashion as the new axis cylinder grows and finally, after several months, it replaces all the destroyed axis. Apparently, the reproduction of new myelin is the result of the combined action of axis cylinder and sheath cells, since without the presence of the axis no myelin is formed. The participation of sheath cells in regeneration has been discussed in the chapter on inflammation. According to Harrison, they have nothing to do with the formation of the new axon.

As a result of direct injury, action of poisonous substances, passive hyperemia and hyperpyrexia, the nerve cells may degenerate. It is also stated that degenerative changes may follow exhaustion and emotional states, but the evidence offered is not conclusive. In a general way it may be said that the cell swells, becomes rounded and the cytoplasm becomes vacuolated. The chromatic granules of Nissl are broken into small fragments, chromatolysis or tigrolysis, and may lose their affinity for dyes, achromatosis. Chromatolysis is regarded by Dye as a general reaction of nerve cells induced by conditions opposed to normal functional equilibrium, and if carried beyond physiological

bounds becomes pathological and may lead to degeneration and death of the cell. The nucleus is displaced to one side of the cell and may be swollen and pale. Occasionally, it may be extruded, with death of the cell. After the extrusion or lysis of the nucleus, chromatolysis and achromatosis proceed, the cell becomes a mere shadow and ultimately disappears by solution and by the action of glial and endothelial phagocytes (neuronophagia).

The central part of the intracellular neurofibrillar network disappears at the time of chromatolysis, and this probably initiates the degeneration of the axis cylinders. Those peripheral fibrils which communicate between processes may remain until degeneration of the cell is advanced. Recovery, however, may ensue if the destructive influence abate before actual cell death occurs. Whereas passive hyperemia produces these changes, interruption of circulation is more likely to produce shrinkage and condensation of cell and nucleus, so that nuclear chromatin and Nissl substance form a homogeneous mass of basophilic substance. Following hyperpyrexia ($42-43^{\circ}$ C.), the cell swells, loses the basophilic character of nucleus and Nissl granules and becomes a more or less homogeneous acidophilic mass.

The changes in cells secondary to lesions of the axons vary in the motor and peripheral sensory neurons, and may be divided into a deteriorative or reaction stage and a reparative stage. In the deteriorative stage the cell shows changes similar to those described as occurring in response to poisons. Some cells may die and disappear, especially if repair of the axon be impossible. Repair may follow any stage short of necrosis. The Nissl granules are restored and assume normal arrangement, the nucleus resumes its normal position and the swelling of the cell gradually subsides (see Nicholson). In the bipolar cells of the peripheral sensory axon in the posterior root ganglia, division of the peripheral axon leads to changes similar to those observed in the motor cells. Division of the central axon may be followed by no change in the cells or by slight atrophy. Nevertheless, division of the central axon may be followed by degeneration of the myelin in the peripheral axon and vice versa.

Corpora amylacea occur in various parts of the brain and cord, secondary to softening, to inflammations, to atrophy and to scar formation. They are round, vaguely laminated, rarely exceed 50 micra in diameter, are acidophilic, iodophilic, and contain glycogen.

Pigmentation.—Certain nerve cells, notably those of the substantia nigra, appear to contain normally, a dark brown granular pigment. Dolley and Guthrie, however, maintain that it is not a normal constituent in any situation, that it is a melanin and that under all conditions, physiological, morbid or senile its genesis is referable to prolonged depression. In man, cattle and fowl, there frequently also occurs a lipochrome of the carotinoid order derived from the food. It is not present in dog, rabbit and swine because their serum does not carry this pigment. Variations in amount of lipochrome content are due to differences in amount of carotinoids in the food. As pointed out in discussing hemorrhage, hematogenous pigments occur in scavenger cells and free in the tissues.

Reactions in Interstitial Tissues.—In response to injuries of the nervous system the cells of the interstitium play an important role. The older confusion in regard to the part played by certain cells has been much clarified by the special staining methods and investigations of Alzheimer, Cajal, del Rio Hortega, Achúcarro, Robertson, Metz and Spatz, Bailey, Penfield, and others. The cells of epiblastic origin found normally are the protoplasmic neuroglia and the fibrillary neuroglia. The protoplasmic neuroglia cell has a large oval

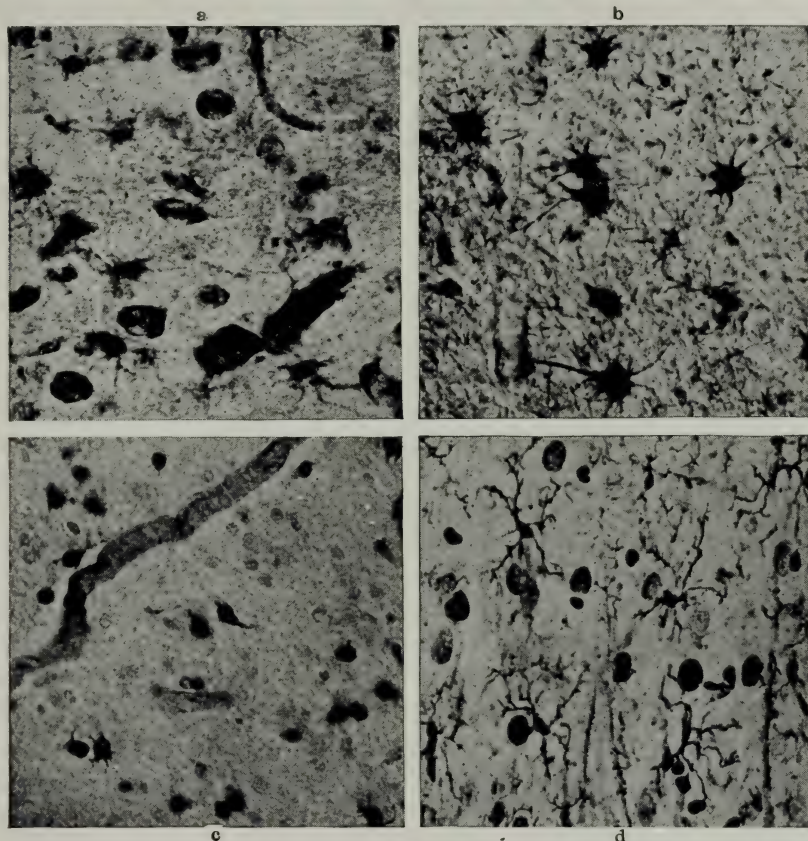


FIG. 409—*a*, Protoplasmic astrocytes, human cerebral cortex. Gold-sublimate method. $\times 300$. *b*, Fibrillary astrocytes. Human cerebral subcortex. Gold-sublimate method. $\times 300$. *c*, Oligodendroglia. Cerebral cortex of dog. Robertson's platinum chloride method. $\times 300$. *d*, Microglia. Cerebral cortex of rabbit. Hortega's silver carbonate method. $\times 300$. From Bailey, P., and Cushing, H., *A Classification of the Tumors of the Glioma Group, etc.*, Philadelphia, 1926.

nucleus with chromatin massed near the nuclear membrane. The large cytoplasmic mass is granular and is prolonged in numerous wide processes, one of which is likely to be attached by a foot-like expansion to a small blood vessel. These cells are not normally fibrillar. In response to inflammation they were supposed by Alzheimer to become ameboid, but it is now known that such an appearance is due to degeneration. The fibrillary neuroglia cell has long been known as the typical neuroglia cell or astrocyte, with small, fairly dense nucleus, well stained finely granular cytoplasm from which fibrils, often branched, ramify into the surrounding spaces. One of the cell processes, from

which most of the fibrils are supposed to originate, has a foot-like terminal in apposition to a small blood vessel. Either of these cells may occur with only a small number of processes or fibrils. In the replacement of defects in the central nervous system the scar is made up of neuroglia of astrocyte type, contributed to principally by the fibrillary neuroglia but also sometimes by transformation of protoplasmic neuroglia with enlargement and production of fibrils.

Two other cell types are observed which Bailey classifies under the heading of mesoglia (?), namely, the microglia and oligodendroglia cells. Although some doubt exists as to their origin, it seems probable at the present time that they are of mesoblastic origin. The nucleus of the microglia is small, oval and has heavy bands of chromatin. The cytoplasm is scanty and from it extend a few long processes, not fibrillæ, which branch dichotomously and show minute spine-like projections at right angles to the stems of the processes and their branches. Under pathological conditions, where debris is to be removed, these cells become phagocytic. The destruction of tissue liberates cell and fiber detritus, neutral fats, fatty acids, soaps, lecithins, cerebrosides and phosphatides (Spielmeyer). The microglia cells multiply by mitotic division, show swelling of the cell body, thickening, shortening and disappearance of the processes, and increase further in size as the debris is ingested. The result is a large cell whose cytoplasm is filled with small lipoidal and fat globules and minor amounts of other debris, which has been given various names including compound granule cells, gitterzellen and scavenger cells. They accumulate about wounds and later stages of inflammatory and other destructive areas, and in response to destruction of tissues in gliomas (Penfield). They transport the ingested material to neighboring capillaries or perivascular spaces. It is probable, however, that many of the cells in these situations, which have the same appearance, are endothelial phagocytes derived from vascular endothelium. Also derived from the microglia cells are the rod cells, or stäbchenzellen, elongated cells found in the cortex under various pathological conditions, parallel to vessels, vertical to the cortical surface, with granular cytoplasm projecting from the long ellipsoidal nucleus. These appear to be special forms of phagocytes.

The oligodendroglia cells, or cells with few dendrites, are probably of mesoblastic origin, although excellent authorities believe them to be epiblastic. The nucleus is somewhat larger than that of the microglia. The cytoplasm is clear or reticulated, small in amount, difficult to demonstrate and is prolonged in a small number of non-fibrillar processes which show little branching and no lateral spines, but with occasional points of nodular enlargement. According to Bailey and Hiller these cells play no part in the reaction to injury, but may possibly constitute an element in tumor formation.

Traumatic Injury.—The brain may be wounded by foreign bodies such as knives, shell fragments or bullets, which penetrate the skull, or by fractures of the skull with displacement inward of fragments of the inner or all tables of the skull. There is destruction of tissues and hemorrhage and edema of the neighborhood. The edema may produce moderate, marked, or even fatal

increase of intracranial pressure. Death may be almost immediate, due to shock, or may be delayed for several days or weeks. Recovery and scar formation may result, or infection may produce meningitis and encephalitis. Injuries to the skull at one point may produce hemorrhage or contusion of the brain at the opposite pole, or fractures of the skull from within outward, the so-called lesions by contrecoup. Direct injuries of the skull or indirect injuries as by falling heavily on feet or buttocks, may, without fracture of the skull, lead to meningeal hemorrhage or to the condition spoken of as concussion. In concussion there is coma, which may be prolonged, usually followed by recovery, sometimes with an intervening period of headache, amnesia and mental confusion. The pathology of concussion is not well understood and few if any lesions are to be demonstrated. In some cases, however, degenerations of cells and of fibers are said to occur. Cases which are clinically concussion may show meningeal hemorrhage, petechiæ in the brain, areas of softening, or contrecoup lesions. Concussion, usually with demonstrable lesions, may rarely lead to internal hydrocephalus.

Partial or complete transverse lesions of the cord may be due to penetrating injuries, to fractures or fracture dislocations of the spine the result of trauma or disease, to tumors, to parasitic cysts and to suppurative lesions. Hemorrhage, or hematomyelia, may be local in meninges or cord or both, but occasionally, starting at the point of injury, the hemorrhage may extend longitudinally, especially in the gray matter, produce acute symptoms like those of syringomyelia, and, if organized, absorbed and cicatrized by gliosis, produce a lesion apparently identical with that of syringomyelia. Interruptions of the cord by either trauma or disease may produce spinal shock with its prolonged depression of reflexes, which is due presumably to a defect in transmission at the synapse of the reflex arc (Sherrington). Degenerations of descending tracts below and of ascending tracts above the point of interruption, ensue. The paralysis affects the bladder, and cystitis, inflammation of renal pelvis and kidney, septicemia or pyemia, and death may follow. At the site of injury, more especially when the cord is crushed, there is swelling, hyperemia and softening of the cord, degeneration and finally necrosis of the gray and white matter, with or without petechiæ, sometimes acute inflammation and reactive gliosis, the condition referred to as compression myelitis. According to Cassirer and others, the lesion appears to be due rather to the severe passive hyperemia from compression of the veins than to the direct pressure upon the cord.

Concussion of the spinal cord may be due to direct or indirect trauma to the spine. The cord may show practically no lesion or may be the seat of edema, of petechiæ and particularly of small areas of softening, either in white or gray matter, and subsequent gliosis (Hassin). More severe injuries may produce contusion, show more marked lesions with degeneration of nerve cells and fibers at the site of injury and the changes of concussion in more remote areas (Hassin).

“War neuroses,” which are neurasthenias, hysterias, psychasthenias, due

to exhaustion and emotional stress, have been incorrectly ascribed to the general bodily compression effects of explosions (Hurst).

Birth hemorrhages are those which occur in the meninges during or shortly after birth. The vessels ruptured are the small tributaries of the large sinuses. Symptoms may be slight or the lesion may be fatal. In some cases the hemorrhage may be due to blood dyscrasia, but according to Sharpe and MacLaire, the great majority are due to trauma of forceps in labor or to prolonged labor, and in these the blood is normal.

Injuries to peripheral nerves may be indirect with the production of a bruise. There are edema and variable degrees of hemorrhage. The myelin may be damaged, with resultant transitory loss of motor or sensory function, or the axis cylinders may also be involved and Wallerian degeneration occur. Division of nerves may be due to knife and projectile wounds, laceration by fragments of fractured bones, or interruption of continuity by abscess, tumors, etc. The resultant changes have been described in the section on degeneration. If a wound be infected, a neuritis may progress along the course of the nerve.

Obstetric paralysis affects especially the arm and is the result of injury during birth. As pointed out by Sever, the injury varies from stretching of the nerve trunks with hemorrhage and edema, to tearing of perineural sheath and of nerve fibers. In the more common upper arm type, the lesion involves the fifth and sixth cervical roots and the suprascapular nerve. In the whole arm type there is involvement in addition of the seventh and eighth cervical and sometimes the first thoracic. Injury to the spinal cord with resultant paraplegia or death is especially likely as the result of breech extractions (Crothers).

Caisson disease or diver's palsy is traumatic in the sense that it is due to release of gas bubbles in the central nervous system. Too rapid decompression on coming out of caissons or diving suits may be followed by temporary or permanent, irregularly distributed, motor and sensory disturbances. Under compression large quantities of nitrogen are absorbed by the tissues, and rapid decompression may discharge the gas so rapidly that bubbles form. The effects on the viscera are insignificant, but in the white matter of the cord may be serious. The gas bubbles press on the surrounding substance and small areas of softening are found in the white matter with marked swelling of axis cylinders and myelin degeneration. The reaction is interstitial rather than vascular and results in gliosis. Since the myelin absorbs a larger quantity of nitrogen than other tissues except fat, the liberation of the gas is correspondingly greater in white matter than in other situations (see Hill).

Circulatory Disturbances.—Localized active hyperemia occurs in inflammations, but a generalized cerebral active hyperemia, in the sense of a notably increased bulk of blood, is unusual because of the large area of venous drainage and of drainage of cerebrospinal fluid. Mental activity presumably is accompanied by an increased rate of blood flow rather than by a true hyperemia. If active hyperemia occur in such conditions as insolation and acute alcoholism, it is not demonstrable at autopsy. Passive hyperemia may be due to local conditions such as compression of veins by tumors and occlusion by thrombosis,

or to general conditions such as heart failure. The brain may be somewhat enlarged, shows dilated meningeal veins, may have a purple tinge and in the cut surface shows numerous fine red or purple points in the position of the vessels in the white matter. This must not be confused with a passive hyperemia of the dependent parts of the brain which often occurs after death.

Temporary general anemia of the brain is usually due to vasomotor disturbances and may cause fainting. Emotional shock or injury to the splanchnic plexus may so dilate the splanchnic vessels that the amount of blood supplied to the head is insufficient. High grade anemias and profuse general hemorrhage may produce cerebral anemia. Local anemia may be due to compression of vessels, as for example, by tumors. Anemia of even short duration may produce cellular changes as described in the section on degenerations of nerve cells. The principal feature grossly is the extreme pallor of white and gray matter and the absence of red punctæ in the cut section.

Edema of the brain may be secondary to prolonged passive hyperemia and may occur in uremia and in acute and chronic alcoholism (Nuzum and Le-Count). Local forms of edema may be seen about tumors, abscesses, hemorrhages, and areas of softening of the brain. The brain is large, moist on outer and cut surfaces and usually pale. There is almost always an excess of fluid in the pia-arachnoid and sometimes a slight excess in the ventricles and in the large lymph sinuses.

Thrombosis and Embolism.—Thrombosis is usually superimposed on arteriosclerosis, commonly in the middle cerebral artery or its branches. It may, however, be due to acute infectious diseases, more especially in childhood, or to blood diseases such as leucemia. Syphilis may produce a gummatous arteritis with secondary thrombosis. Rarely trauma is a cause of thrombosis. If the lumen of the artery be reduced, the area supplied becomes the seat of atrophy with degeneration and disappearance first of cells and then of nerves, and a replacement gliosis and fibrosis. In this way, numerous large and small areas of cerebral cortex may be the seat of the so-called arteriosclerotic atrophy. If the vessel be occluded, necrosis results in the same manner as following embolism.

Embolism may be due to the lodging of a fragment of clot from acute endocarditis, cardiac thrombosis, thrombi on arteriosclerotic plaques or in aneurysms, fragments of diseased aorta, or destructive lesions of the lungs. Emboli lodge most frequently in the middle cerebral artery or its branches, but other arteries may be affected. Fat embolism is often widespread in the brain and may be the cause of convulsive symptoms, but usually is fatal before secondary changes occur. Both thrombosis and embolism may produce the clinical syndrome called apoplexy, thrombosis with gradual onset, embolism with abrupt onset. Hemorrhage is the most common cause of apoplexy, usually with onset somewhat less abrupt than in embolism. Thrombosis and embolism lead to infarction of the brain, usually referred to as softening of the brain or encephalomalacia. Rarely, but more especially in childhood, occlusion of veins may produce softening.

Encephalomalacia.—Fresh areas of softening may not be determinable grossly until after the brain is properly hardened in a fixative. They are then found to be softer and more friable than the surrounding tissue. The conical shape of the infarct with base toward the cortex may be apparant if a large artery be occluded, but often the vessel is of small size and centrally situated so that the area of softening is generally globular. If several days have elapsed, the softened area may be swollen and, if peripheral, the convolutions may be flattened and pale. The involved area is moist, soft, friable and bulges in the cut surface. Microscopically, all stages of degeneration to complete necrosis of nerve cells and fibers are found, with cell detritus and fragments of myelin, but the striking feature is the appearance of the compound granule or scavenger

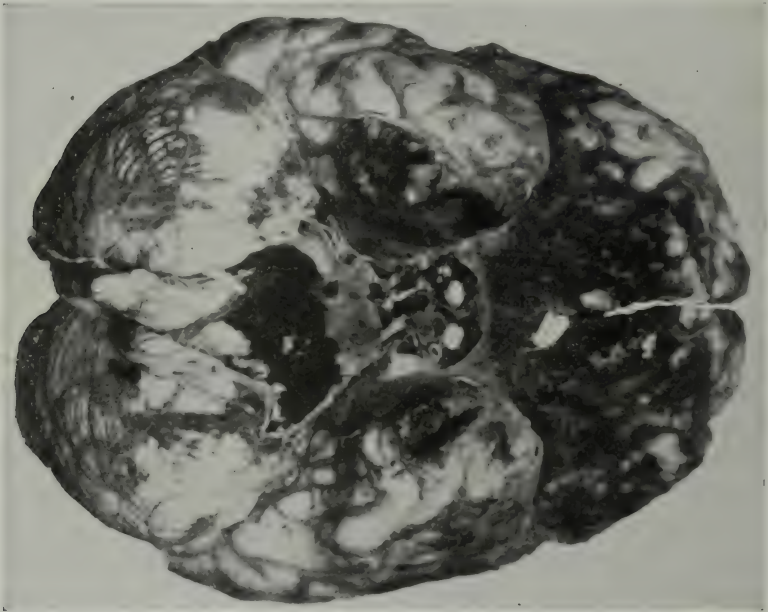


FIG. 410—Meningeal hemorrhage, the result of falling on buttocks.

cells described above. Hemorrhage does not seem to be so constant in cerebral infarcts as in those of other organs, but not infrequently the area of white softening later becomes red as the result of diffuse bleeding. Subsequently, as the blood degenerates, the area becomes yellow. By this time, the necrotic area has liquefied and glial reaction has become so marked that a cyst is formed. In minute areas no such cystic stage occurs because organization fills the defect, but if the infarct have a diameter of about one centimeter or more, cyst formation results. The cyst content may be cloudy and granular or may be almost clear, of brown or yellow tinge or nearly colorless. If the small area be organized, the residual granular and crystalline blood pigment gives it a brown color. If cyst formation occur, the cyst wall is similarly pigmented. Scavenger cells may be observed for a long period after the original softening, but in diminishing numbers. In small areas the neuroglia may be preserved

but in larger areas it undergoes necrosis. The scar or cyst wall is built up by fibrillary neuroglia and by the growth of mesoblastic tissue which accompanies the blood vessels. The tract degenerations will be discussed with those which follow hemorrhage.

Hemorrhage.—Hemorrhage may take place in the meninges, the brain substance or the ventricles. Traumatic hemorrhage may occur in the pia arachnoid space as the result of direct or indirect injury. In many cases it is the result of rupture of veins and the blood mass is relatively small, produces slight or no pressure symptoms and is readily resorbed. Such subdural hemorrhage of arterial origin may be large and fatal but seldom occurs without pre-existent disease of the arteries. Extradural hemorrhage is most often due to skull fracture. Traumatic hemorrhage into the substance of the brain may be due to penetration of missiles, to fragments of fractured skull, or is indirect in the lesion of contrecoup. Hemorrhage into the brain substance, not traumatic, may occur in acute infectious diseases, especially the hemorrhagic forms, or in blood diseases of purpuric type. Such hemorrhages are usually small and multiple. The larger solitary, or rarely multiple, hemorrhage which produces apoplexy and hemiplegia is most commonly due to rupture of one or more of the small lenticulo-optic or lenticulostriate arteries, which branch off at right angles from the middle cerebral artery. As a rule, both disease of the arteries and high blood pressure are necessary to produce rupture. These small arteries, because of their direct origin from a larger vessel are subject, at least at their points of origin, to higher intravascular pressure than if they were the ordinary dichotomous branches. The disease is usually arteriosclerosis, but acute arterial disease, syphilitic gummatous arteritis and aneurysms may furnish a point of diminished resistance to intravascular pressure. Since arteriosclerosis is a disease of late middle and advanced life, so also is apoplexy. Apoplexy in the fourth decade is often ascribed clinically to syphilitic arteritis but certainly many such cases are due to rupture of only slightly diseased or practically normal vessels in cases of hypertension, especially that form due to the so-called diffuse hyperplastic sclerosis. Aneurysms of the cerebral arteries are not common. Occasionally intimal arteriosclerosis or syphilitic arteritis may lead to aneurysm formation. Mycotic aneurysms may follow acute infectious diseases. The larger aneurysms may produce local or general pressure symptoms and may rupture either into the meninges, the brain substance or the ventricles. Multiple miliary aneurysms are rare. Numerous small

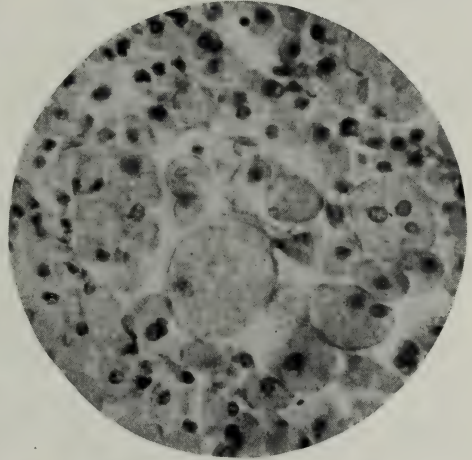


FIG. 411.—Scavenger cells or compound granule cells in the margin of an area of encephalomalacia.

hemorrhages into the perivascular space and surrounding brain substance, often globular in form, may be mistaken for miliary aneurysms. Vessels other than the basal branches of the middle cerebral may rupture and the hemorrhage is correspondingly distributed. Ventricular hemorrhage is practically always due to penetration of an intracerebral hemorrhage through the ependyma and the blood may pass on into the subdural space of cord and brain.

As mentioned above, hypertension in younger individuals, physically active and with hypertrophic myocardium, may produce apoplexy with little disease of the cerebral vessels. Nevertheless, the disease of the cerebral arteries of more advanced life rarely leads to rupture unless there is some elevation of blood pressure such as that due to arteriocalillary disease, chronic glomerulonephritis, or constitutional hypertension. This seems to be especially true if the

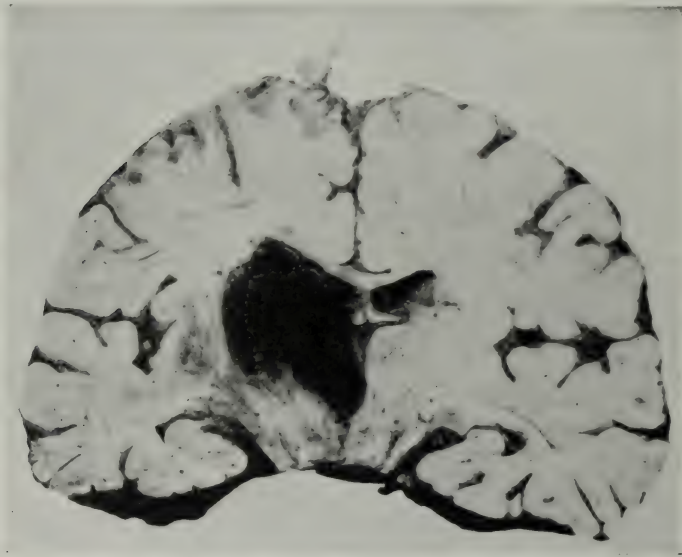


FIG. 412—Hemorrhage in cerebrum involving internal capsule.

pressure be suddenly augmented by physical stress or emotional excitement.

According to Ernst the larger hemorrhages occur, in diminishing order of frequency, in the basal ganglia, the external and internal capsule, corona radiata, cortex, pons, cerebellum and rarely in crura and brain stem. Although small aneurysms may be found in the affected vessels, the studies of Lindermann indicate that the actual hemorrhage is from several minute ruptures of the vessel walls rather than rupture of these aneurysmal dilatations. As the blood extravasates, it destroys nerve substance and compresses the surrounding area. The hemorrhage may be minute, or may vary from a centimeter in diameter to a mass so large as to occupy almost an entire hemisphere. It is usually fairly well defined and may be surrounded by an area of edema or by a number of small punctate hemorrhages, the latter probably due to rupture of capillaries from the sudden increase in pressure resulting from the large hemorrhage. The blood rapidly clots and the cut surface is dark red and rela-

tively dry. Recent hemorrhages may bulge in the cut surface, but in the course of time the clot contracts, the serum is drained away and the cut surface retracts. Microscopically, the neighborhood of recent hemorrhages shows an infiltration of mononuclear cells and a few leucocytes. Scavenger cells appear and phagocytose the debris of tissue and myelin. The break down of blood furnishes both hemosiderin and hematoidin, which for a time are within phagocytic cells. There is a reactive gliosis and fibrosis and the hemorrhage becomes cicatrized if small, or encysted if large. The cyst is filled with limpid or thick fluid, usually brown or yellow in color and the cyst wall is of similar but usually deeper color, due to the pigment which now lies free between cells and fibers. Persistent blood vessels which have undergone thrombosis and organization may remain as bands in the cavity of the cyst. The scar may be multilocular or lacunar in character.

The usual hemorrhage interrupts either directly or by pressure the anterior part of the internal capsule.

The extent of interruption is reduced as edema decreases and the clot contracts. Nevertheless, in the more extensive lesions there is a consequent degeneration of the upper motor neuron, extending through pons, medulla and cord, which involves direct and crossed pyramidal tracts. The partial or complete coma of the apoplectic seizure is presumably due either to



FIG. 413—Hemorrhage in pons.

the general increase of intracranial pressure, or to pressure upon the healthy side by the swollen diseased side. The conjugate deviation of head and eyes toward the side of the lesion is probably due either to involvement of the laterogyric center of Horsley or to hemianopsia (Foix). The early flaccid paralysis and decreased reflexes are probably due to cerebral and spinal shock, but as this is recovered from, the interruption of the inhibitory influence of the upper neuron results in spastic paralysis and contractures. Disturbances of sensation may occur when the posterior part of the internal capsule is involved. *Decubitus ulcers* commonly occur, but their exact origin is subject to discussion. Pressure anemia and trophic disturbances are thought to play an important part, but certain observers think that they are due principally to infection of the buttocks as the result of incontinence of urine and feces. The same general train of events is also associated with encephalomacia due to thrombosis or embolism.

Sinus Thrombosis.—Severe acute and chronic infectious diseases, prolonged exhausting diseases, and blood diseases may be complicated by throm-

bosis of the large venous sinuses of the cerebrum and meninges. This occurs especially in infants and the aged. It is called marantic or primary in contrast to the secondary form, where the venous thrombosis is secondary to some other lesion, as for example, obstruction by tumors, or more frequently extension of inflammatory lesions. Inflammations of the bones of the skull, embolic or secondary to inflammations of the face, mouth, nose or air sinuses, inflammations of the meninges or abscesses within the skull cavity, may produce sinus thrombosis. Probably the most common cause is suppurative otitis media which extends to the mastoid air cells and thence to the lateral venous sinus. The primary cases show more or less organized mixed clots, which often extend into tributary veins. In some instances a hyperemic area of encephalomalacia may occur. In the secondary cases the thrombus may be simple or may suppurate, and as a result brain abscess or purulent meningitis may occur.

Circulatory Disturbances of the Spinal Cord.—Hyperemia may occur in the

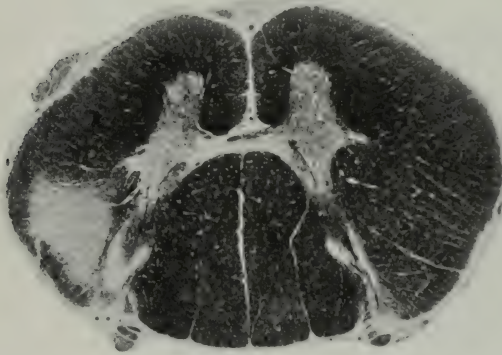


FIG. 414—Cross section of cord, showing degeneration of direct pyramidal tract secondary to cerebral hemorrhage. Weigert-Pal. Microtessar 32 mm. Courtesy of Stanley Cobb, M.D.

spinal cord under the same circumstances as in the brain. Passive hyperemia may also be induced by the compression of traumatic lesions or tumors. Small areas of myelomalacia are not rare, and result from minute arterial emboli. Hemorrhage into the cord, or *hematomyelia*, is usually traumatic in origin and only rarely due to rupture of diseased vessels by high blood pressure.

The hemorrhage is usually in the gray matter, probably because it is more richly vascular than

the white matter, and extends longitudinally as noted in the section on traumatic injuries. *Hematorrhachis* may be extradural or subdural. The former may be traumatic or may be the result of rupture of an aneurysm or due to violent convulsions. Subdural hemorrhage may originate in the head, it may be due to direct or indirect injury of the spine, or it may complicate any of the various hemorrhagic diseases. The extrameningeal hemorrhages rarely produce pressure symptoms because of the ready escape of the blood outward. Subdural hemorrhages may occasionally lead to compression of the cord. Edema of the cord may result from inflammations and from passive hyperemia. Edema of the meninges is usually secondary to excess fluid drainage from cerebral ventricles or meninges.

Atrophy may be local as the result of arteriosclerosis or of pressure, or may be general as in chronic poisonings, prolonged exhausting diseases, general paralysis and in senility. The brain is reduced in size and weight. Atrophy is more severe in the gray matter and the convolutions are small, narrow and of deep gray color. The basal ganglia may be noticeably reduced in size. The

brain is usually of increased consistency. The meningeal and ventricular fluid is increased in amount and the meninges are often fibrosed. The ganglion cells are reduced in size and often exhibit degeneration with chromatolysis, pigmentation, displacement of the nucleus, and subsequent death. The myelin of the nerves may be reduced in amount. Replacement overgrowth of fibrillary neuroglia is practically always present.

Hypertrophy of nerve cells is extremely difficult to evaluate in human material, but Collier's careful studies indicate that it occurs in dogs as the result of prolonged physical exercise.

Inflammations.—**Meningitis** may be acute or chronic and may affect either the pia-arachnoid, leptomeningitis, or the dura, pachymeningitis. Suppurative external pachymeningitis is secondary to lesions of the bones of the skull,



FIG. 415—Large area of cortical atrophy due to arteriosclerosis.

as osteomyelitis or more especially inflammation of air sinuses. It may spread laterally but is more often confined in the form of an extradural abscess. It may extend through the dura and produce leptomeningitis, brain abscess or sinus thrombosis. It is said that internal hemorrhagic pachymeningitis may be of inflammatory origin, although our own cases show no true inflammation, or may be secondary to passive hyperemia as in heart disease. It may be secondary to atrophy of the brain and occurs in general paralysis, chronic progressive chorea and chronic poisonings. The lesion is usually on the vertex and may be bilateral or unilateral. Attached with variable degrees of firmness to the inner surface of the dura, is a thin laminated film of red, brown or yellow color. The inner layer of the dura is rich in capillaries which bleed easily. A layer of blood spreads over the inner surface, sometimes with and sometimes without leucocyte infiltration, and with fibrin deposit. This undergoes organization by fibroblasts and blood vessels, and blood pigment is deposited. A second layer is formed and the process repeats itself, each succeeding layer more recent in

appearance than its predecessor. The process may be arrested and remain as a dense, adherent, brown or yellow layer of fibrous tissue. Pachymeningitis cervicalis hypertrophica is a rare lesion, in which the dura and pia-arachnoid surrounding the cervical enlargement of the cord become the seat of dense fibrosis, may become calcified and even ossified. Its cause is unknown.

Acute leptomeningitis may be serous, fibrinous, purulent or hemorrhagic. Serous meningitis is not common at autopsy but the clinical examination of spinal fluid shows that it frequently precedes the purulent form. Fibrinous meningitis is most often seen in acute tuberculous infection of the membrane. Purulent meningitis is common. Hemorrhagic meningitis may occur in fulminant form and is associated with the hemorrhagic type of infectious diseases,

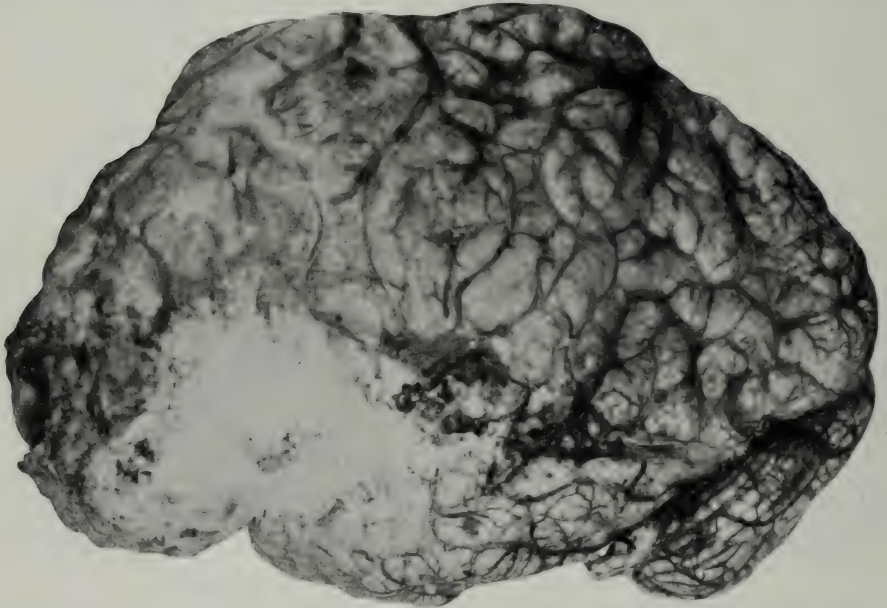


FIG. 416—Abscess of temporal lobe of brain, with associated acute purulent meningitis. Army Medical Museum, 30804.

blood diseases, etc. Except in epidemics of meningococcal cerebrospinal meningitis, the most common organisms are the pyogenic cocci, especially streptococcus hemolyticus, and the pneumococcus. A wide variety of other organisms may cause the disease including bacillus typhosus, bacillus influenzæ and bacillus coli. Streptococcus meningitis may be apparently primary or may complicate measles, influenza, pneumonia, septicemia, etc. It is not always possible to prove the existence of a pneumonia preceding pneumococcus meningitis, or typhoid fever before a typhoid bacillus meningitis. Acute meningitis may follow surgical or accidental trauma and may cover only the hemisphere of the injured side. The same is true of meningitis due to inflammations of the air sinuses, particularly those of the mastoid process. Organisms may gain entrance through the blood stream. This may be true in demonstrable septicemia and pyemia, but often, although blood transport is the only

method of explanation, blood cultures remain sterile. The lesion may also result from an infective sinus thrombosis. It is thought that in some cases, the organisms, either grow along or are transported along the olfactory nerves as they pass through the cribriform plate of the ethmoid. Inflammations of the spinal meninges may extend from the cerebral meninges or may be primary, due to trauma with infection and to blood transport.

The distribution of the exudate depends somewhat upon the mode of origin, and it may occupy the vertex or base of the brain or the spinal meninges, and may involve all three situations. Hyperemia is marked and there may be petechiæ. The exudate may be serous in character, limpid but cloudy, containing numerous leucocytes, desquamated endothelial cells, fibrin threads and bacteria. The meningismus of acute infectious fevers may be due to serous meningitis, but since many cases come to autopsy without meningitis of any type, the symptoms then may be purely toxic in origin. The purulent exudate is made up largely of leucocytes, normal and in various degrees of degeneration, and contains also mononuclear cells, tissue debris and bacteria, but usually little fibrin. The gross color depends in part upon the nature of the bacteria, but ordinarily is pale yellow. Pyocyaneus gives its characteristic green color and the exudate in pneumococcus meningitis is often of pale green tinge. Usually the inflammation is confined to the meninges with only hyperemia in the underlying nerve substance, but in the suppurative varieties there may be extension into the brain substance, meningo-encephalitis, or into the cord substance, meningomyelitis. Hemorrhagic meningitis may be due to hemorrhagic infections or to anthrax bacilli. The hemorrhage may be punctate or widespread and may be massive. Most such cases are fulminant and both grossly and microscopically the inflammation may be masked.

In addition to irritation of cortex, nerves or cord, by the inflammation, there may be an increase in intracranial pressure. This may be due to accumulation of exudate or adhesions in the cisterna magna, to occlusion of the ventricular outlets by exudate, for the process may extend into the ventricles by way of the choroid plexus, or may be due to occlusion of drainage by the arachnoidal villi. In some cases edema of the brain may be sufficient to interfere with drainage, and in others the pus may become so thick and viscid that flow of fluid is obstructed.

Epidemic Cerebrospinal Meningitis.—This disease may be sporadic, endemic or epidemic. It is due to the meningococcus intracellularis of Weich-



FIG. 417.—Epidemic meningitis showing meninges dipping into a sulcus, with a rich inflammatory exudate. Microtessar 43 mm.

selbaum, a small gram negative diplococcus, often phagocytosed by the leucocytes of the exudate. Its mode of entry into the meninges is not clear, although the fact that it is present in the nasopharynx of victims and carriers, suggests strongly that it enters through the cribriform plate of the ethmoid. It is probably transmitted by droplet infection. The inflammation usually begins at the base of the brain, whence it extends anteriorly to the temporal and frontal lobes, posteriorly over the cerebellum, laterally over the Sylvian fissure and vertex, and inferiorly along the brain stem and cord. The exudate is richly purulent, thick and of yellow or greenish-yellow color. The nerve substance is not frequently involved. Microscopically, the leucocyte is the principal cell and often contains large numbers of organisms. As the process becomes subacute and chronic, more and more lymphocytes and large mono-

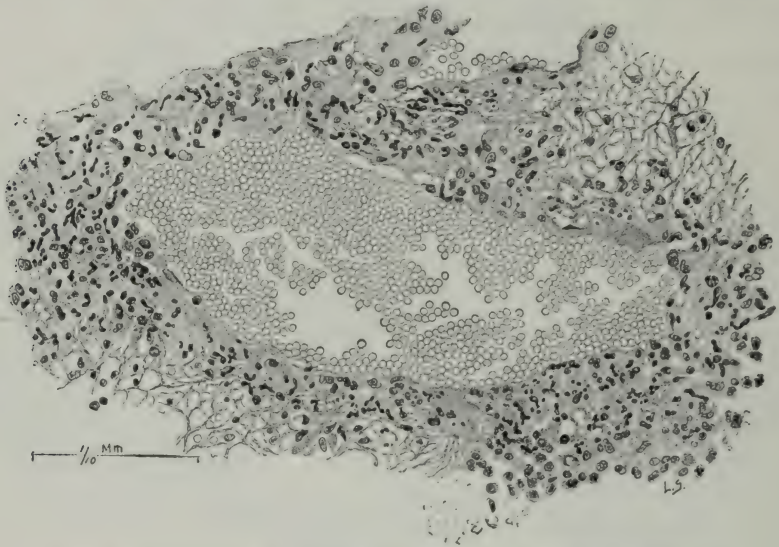


FIG. 418—Hyperemia and cellular exudate of acute purulent meningitis.

nuclear cells are found. If recovery ensue, there may be a residual fibrosis, often called chronic posterior basic meningitis, with thickening of the meninges over the pons, medulla and inferior surface of the cerebellum. Here it may involve the cisterna magna and prevent drainage of the ventricles. Thus internal hydrocephalus may more or less abruptly kill patients who seem to have survived the acute disease.

Chronic leptomeningitis may occur upon any part of the brain and cord, in the course of chronic alcoholism, lead poisoning, chronic nephritis and heart disease, or over lesions of the nervous substance. It may be simply a fibrosis which produces a thick, white, dense, adherent area in the meninges, or may also show an associated serous exudate containing a few lymphocytes. Syphilis may produce a condition similar grossly, but with special features microscopically. Cicatrization of a preceding acute meningitis may give much the same appearance as a chronic meningitis.

Torula Meningitis.—In addition to the possible involvement of meninges and brain in oidiomycosis and coccidioidal granuloma, several cases have been recorded of invasion by *torula histolytica*. It may produce in the soft meninges a chronic inflammation, and in the brain there may be either granulomatous lesions or diffuse perivascular infiltration of organisms, with lysis of brain substance and little or no inflammatory reaction. The organism appears to have a special affinity for the central nervous system both in man and in the experimental disease in animals (Stoddard and Cutler, Shapiro and Neal).

Encephalitis.—This may be suppurative or non-suppurative and is to be distinguished from encephalomalacia. *Suppurative encephalitis* or abscess of the brain is due to infection which may enter in various ways. Infected surgical wounds, compound fractures, and the entry of infected missiles may be followed by abscess. The suppuration, however, may be delayed several days after the trauma. In civil life, suppuration of middle ear and mastoid process is the most common cause of abscess. The abscess may be in continuity with the ear disease, may be separate, lying in the temperosphenoidal region or cerebellum of the same side, or may occur in the opposite side, probably due to lymphatic transmission of the organisms. Other forms of suppurative bone disease of the skull may produce abscess. Suppurative sinus thrombosis and, rarely, suppurative meningitis may produce abscess, although in the latter instance it is often difficult to determine which is primary, for an abscess rupturing on the surface may produce a widespread meningitis. Multiple abscess of the brain may complicate almost any of the acute infectious diseases, including the exanthemata, diphtheria, rheumatic fever, typhoid and typhus fevers, anthrax, glanders, and the pyogenic septicemias and pyemias. In many instances the abscesses are microscopic in size and perivascular in arrangement. In pyemia, however, they may be numerous and large. Destructive diseases of the lung such as purulent bronchitis and bronchiectasis, pulmonary abscess or gangrene may be complicated by abscess of the brain, usually single and in the left side. A very few cases are without demonstrable origin and are called idiopathic. In certain cases trauma, not sufficient to break the skin, may precede brain abscess and there may be no other apparent cause, but it is difficult to understand the relation between the injury and the abscess, and for the present such cases might well be included in the idiopathic group. In addition to various aerobic and anaerobic bacteria, the lesion may be caused by streptothrices.

The gross appearance depends somewhat upon the cause. Traumatic abscess shows the hemorrhage due to the injury. In certain infectious diseases, the abscess may be hemorrhagic, as for example, in scarlatina, pertussis, influenza, anthrax and streptococcus endocarditis. The pus is usually creamy and yellow but may show other characters and colors when caused by special organisms. Similarly, the odor varies. In the more recent abscesses the surrounding brain substance is edematous and the seat of encephalomalacia. Later, a wall of organization is present with an outlying area of softening. Surrounding hyperemia may or may not be present. Ultimately a cyst or scar may

result. Depending upon the extent and severity of the abscess or abscesses, the brain may be large and edematous with flattened convolutions.

Microscopically, the course of the abscess is much the same as elsewhere, with primary hyperemia and necrosis of brain substance, followed by exudation and the processes which lead to encapsulation or cicatrization. The nerve cells and fibers show the ordinary degenerative changes, which progress to necrosis. Three more or less distinct layers can ordinarily be made out in the larger abscesses. The center of the abscess is made up of necrotic brain substance, leucocytes, both normal and degenerate, bacteria and sometimes blood or blood pigment. The second zone is provided principally by mesoblastic granulation tissue derived from the blood vessels. Intermingled with the fibroblasts are tissue debris, lymphoid and large mononuclear cells and scavenger or compound granule cells. The third zone is that of glial reaction, where in the earlier stages, various degenerative forms may be encountered including the "ameboid" form. Multiplication of glia cells is by mitosis, and multinucleated forms may result. Ultimately, the proliferation of fibrillary neuroglia produces a fairly dense zone of fibrillar gliosis. The surrounding blood vessels may show perivascular infiltration, at first of leucocytes and later of lymphoid cells. The surrounding nerve cells may show slight degenerative changes.

Non-suppurative Encephalitis.—The outstanding example of this is *epidemic encephalitis*, or *encephalitis lethargica*. The cause of this disease is not finally proven, although the studies of Loewe and Strauss and of McIntosh and Turnbull and others indicate that a filterable virus may be obtained from brain, spinal fluid and nasopharyngeal washings, which is said to produce symptoms and lesions in monkeys and rabbits. Similar lesions, however, may be found non-experimentally in the brains of rabbits (Flexner) and of monkeys (Lucké), which throws doubt upon the specificity of the lesions which are observed after experimental inoculation. Oliver, confirming Levaditi, points out that the non-experimental rabbit lesion can be distinguished from inoculated epidemic encephalitis by differences in the character of the lesion and by the presence in the former of protozoon-like microorganisms. On this basis it seems that the virus studied and apparently cultivated by Loewe and Strauss is specific. Its relation to the filterable viruses of acute anterior poliomyelitis and of herpes is not yet clear.

Grossly, the brain may be swollen, the superficial vessels are distended and the gray matter is of light pink color. In cross section the pink tinge of the gray matter stands out in marked contrast to the white matter. The latter shows distended vessels. Small, or rarely larger, hemorrhages may be observed on the outer surface or in any part of the cut surface. The gray matter of the cord may be pink and small hemorrhages may occur. Less severe cases may show only hyperemia at the base of the brain, perhaps with hemorrhage.

Microscopically, the lesions may show varying stages in the same brain, usually with the most advanced changes in the basal ganglia, pons and medulla. The earliest change is a profound hyperemia, often with blood in the perivascu-

lar space, and small hemorrhages in the surrounding tissue. In one of our cases a small amount of fibrin was observed in a perivascular space. Subsequently, the most notable feature, although it is said to be absent in some cases, is a crowding of lymphoid cells with a few plasma cells in the perivascular spaces, especially in relation to venules, and even the capillaries may show a surrounding row of lymphoid cells. Polymorphonuclear leucocytes play practically no part in the reaction. Thrombosis of venules and of arterioles may occur and with it a small area of encephalomalacia. The nerve cells show chromatolysis which in most cells is recovered from, but a few undergo more marked degeneration and death. Phagocytes, probably endothelial, remove the cell debris (see Marinesco). Similar degeneration may occur in the gray matter of the cord, but perivascular infiltration is rarely seen. The pia-arachnoid, more especially at the base of the brain, and sometimes in the cord, may show a

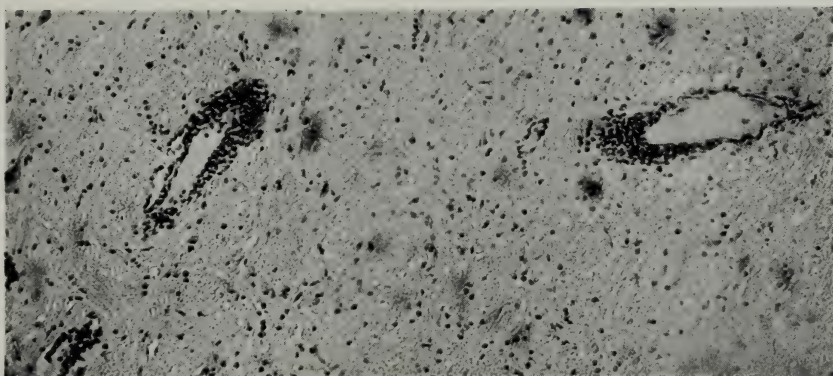


FIG. 419—Perivascular infiltration of lymphoid cells in epidemic encephalitis.

slight edema, slight diffuse infiltration of lymphoid cells and a few collars of perivascular infiltration (see Tilney and Howe).

The clinical symptoms show considerable variation, and owing to our inadequate knowledge of the detailed functions of the basal ganglia, it is difficult to correlate symptoms and lesions. For example, the lethargy is variously ascribed to general intoxication, to hydrocephalus and to disturbance of the hypothetical sleep center. Various paralytic phenomena may be due to thrombosis, to hemorrhage or to areas of softening. The Parkinson syndrome, with or without tremors, which sometimes persists after the acute attack, may be due to destruction of nerve cells.

Other lesions of the brain are often included with the non-suppurative forms of encephalitis. In some instances at least, such conditions are not inflammatory. Thus, acute alcoholic polio-encephalitis is due principally to multiple minute hemorrhages with reparative changes (see Southard). The same misconception applies to polio-encephalitis of other origin (Hassin), and perhaps also to poliomyelo-encephalitis and to acute primary encephalitis of childhood (Sachs).

Myelitis.—Inflammation of the spinal cord may be suppurative or non-suppurative. The latter, however, may be exudative even though not purulent. *Abscess* is much less common in the cord than in the brain. The causes, however, are much the same except that lymphatic transmission may play a more striking part in the cord. Abscesses of thorax, abdomen and pelvis, may extend to the cord by way of the lymphatics which accompany the spinal nerves. The abscess of the cord is most often situated in the posterior horn of the gray matter, often spreads longitudinally and shows little tendency to encapsulation.

Non-suppurative acute myelitis is generally of infectious origin. Acute infectious fevers seem to play an important part, but the disease may be without ascertainable cause. A so-called toxic myelitis, less severe than other forms, may be a manifestation of toxemia of pregnancy. In the infectious forms the causative agent may gain access by direct extension as from vertebrae and meninges, by blood transport as in pyemia, or by ascent along perineural lymphatics as from pelvic abscess.

According to distribution, myelitis may be either transverse, diffuse, or disseminated. Transverse myelitis involves the entire substance of the cord and extends through several segments, usually in the thoracic region. Diffuse myelitis is irregularly distributed throughout a considerable extent of the cord. In acute disseminated myelitis several disconnected areas are involved. With the more extensive lesions the meninges are also inflamed and there is a meningomyelitis. According to the character of the lesion, myelitis may be degenerative or parenchymatous, exudative or hemorrhagic.

In the earlier stages a cord, the seat of degenerative myelitis, is swollen and pale. On section, distinction between gray and white matter is lost and the white pulpy mass bulges over the cut margin. Subsequently, the cord is soft, gray in color and shrunken. In the exudative form minute punctæ of hemorrhage may be observed. In the hemorrhagic form the hemorrhage is more pronounced and in the later stage of shrinkage, the cord may show much pigmentation. Secondary tract degenerations are found above and below the lesion. Essentially the same changes may be observed in the more focal forms of myelitis.

Microscopically, there is marked hyperemia. In the degenerative and hemorrhagic forms, but especially in the exudative form, there is cellular exudation, in variable proportions, of leucocytes, lymphoid and plasma cells. Hemorrhage may be found microscopically in the degenerative form, but is more apparent in the exudative, and pronounced in the hemorrhagic form. The nerve cells show all stages of profound degeneration followed by necrosis. The nerve fibers show first swelling of sheath and axis cylinder, and then fragmentation of myelin and disappearance of axis cylinders. Secondary degenerations may occur in cells connected with the destroyed fibers but remote from the field of inflammation. Scavenger cells may be numerous and are often grouped around blood vessels. Thrombosis of blood vessels may produce small areas of myelomalacia. The neuroglial cells show swelling, vacuolization, homogeneity, and ultimately disappear. Others may be large and multinu-

cleated. Neuroglia proliferates and ultimately constitutes the larger part of whatever cicatrization occurs.

Acute anterior poliomyelitis is often called infantile paralysis and Heine-Medin disease. Known for many years to occur in epidemic form, it was shown by Levaditi and Landsteiner to be transmissible, and found by Flexner and Lewis to be due to a filterable virus. The virus is recoverable from cord, spinal fluid, nasal washings, and in a monkey has been recovered from the blood. It is readily killed by heat but resistant to cold. Noguchi cultivated the virus and found minute globoid bodies not exceeding 3 micra in diameter, arranged in staphyloid clumps and short chains. These can be identified in the lesions. Levaditi and Landsteiner and others found that the serum of convalescents has a protective power, which Flexner and Lewis found in the blood as early as the sixth day of the disease, but an artificial hyperimmune serum has not been produced (Aycock and Amoss).

The lesions are principally in the cord, not infrequently also in the medulla (McEachern), pons and dentate nucleus of the cerebellum and sometimes in other parts of the brain. Grossly, in the earlier stages the cord is swollen, edematous and on cross section shows a bulging surface with pink gray matter. The gray matter of the brain is also likely to be pink. Gross hemorrhages are unusual. The meninges may be hyperemic, but show no grossly visible exudate. Microscopically, hyperemia is conspicuous, small hemorrhages may be seen and there may be perivascular infiltration of small mononuclear cells in cord and meninges. In the cord, especially in the gray matter, and in the spinal meninges there may be a diffuse infiltration of small mononuclear cells and a few large mononuclears, occasionally arranged in clumps and in rings around nerve cells. These cells are variously supposed to be lymphocytes, polyblasts, glia cells and adventitial cells (Wickman, Strauss). Scavenger or compound granule cells may persist for a long time. Polymorphonuclear leucocytes are found only when small areas of tissue are the seat of necrosis (Peabody, Draper and Dochez) and may accumulate in small abscess-like foci. The nerve cells, especially of the ventral horns, but also of Clark's column and the dorsal horn, show various degrees of degeneration and some undergo necrosis (see Cone). Phagocytosis of the cells by small and large mononuclear cells may be prominent. The white matter is much less affected than the gray matter but

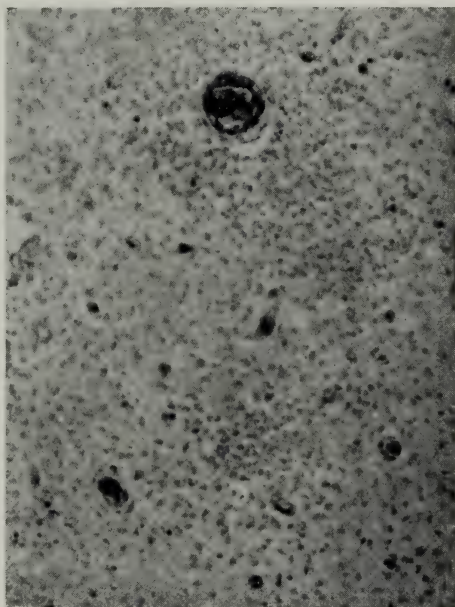


FIG. 420—Rich infiltration of mononuclear cells in anterior horns of cord in epidemic poliomyelitis.

Wallerian degeneration can be found in some of the fibers. Similar changes are sometimes to be found in brain stem, cerebellum, and brain, but usually are less intense in higher areas. As healing progresses, the acute reaction becomes less severe and the only change observable grossly is reduction in size of the anterior horns. Cicatrization is almost solely by gliosis, which replaces destroyed ganglion cells and areas of necrosis, and surrounds degenerate nerve tracts.

In the acute stage there is often well marked lymphoid hyperplasia of intestine, spleen and lymph nodes, sometimes with necrosis, cloudy swelling of parenchymatous viscera and rarely focal necrosis of the liver.

Clinically and pathologically, the condition is clearly defined as an acute infectious fever. The resultant flaccid paralysis and muscle atrophy are due to the destruction of cord cells. Both clinically and pathologically acute poliomyelitis and epidemic encephalitis may be confused. Poliomyelitis, however, is usually of more rapid onset and resembles more closely an acute infection. It is more likely to show the pathological signs of acute infection in the viscera (Burrows) but if, as sometimes happens, the case of epidemic encephalitis has an associated infection, especially pneumonia of influenzal type, the organs may show cloudy swelling and lymphoid hyperplasia. Hassin points out that both degeneration of cells and fibers and inflammatory reaction are more profound in poliomyelitis, and that, whereas in both diseases the lesions may involve the entire central nervous system, they decrease in intensity toward the brain in poliomyelitis and toward the cord in encephalitis. The viruses of the two diseases are apparently different. The monkey is somewhat refractory to the virus of encephalitis and more susceptible to that of poliomyelitis (Loewe and Strauss). Apparently the convalescent protective sera do not show crossed reactions.

Chronic myelitis probably represents entirely the healing and healed stages of various acute degenerative and inflammatory lesions of the cord.

Neuritis.—This term is applied to lesions of the peripheral nerves, which may be either predominantly degenerative or inflammatory. A single nerve may be affected, mononeuritis, or several may be involved, polyneuritis or multiple neuritis. Anatomically, parenchymatous or degenerative, and interstitial forms occur. Predisposing causes seem to be present in many cases of both types, and include prolonged exhausting diseases and the rheumatic or gouty diathesis.

Interstitial neuritis usually involves only one nerve and may apparently be due to exposure to cold, trauma, pressure of tumors or joint displacements, the lymphatic absorption of injurious substances from neighboring foci of inflammation, or direct infection by bacteria. Grossly, the nerve may be hyperemic and exhibit diffuse or nodular swelling. Microscopically, there is hyperemia and often edema, together with infiltration of small and large mononuclear cells, some of which may contain cellular debris and products of myelin degeneration. As the result of pressure, the myelin sheaths may degenerate but the axis cylinders are rarely affected. Pain may be severe, local or referred,

or may be neuralgic. Healing is accompanied by fibrous tissue growth and restoration of myelin sheaths. Many neuralgias show no anatomic basis in the nerves, in others there is neuritis, and in trigeminal neuralgia, or tic douloureux, the Gasserian ganglion may show fibrosis.

Parenchymatous or degenerative neuritis may be mononeuritic but is often polyneuritic. It may be caused by bacterial products, especially diphtheria toxin, by inorganic poisons, especially arsenic, lead and other metals, or by organic poisons such as dinitrobenzol and carbon monoxide. Some cases show nothing other than the supposed predisposing causes mentioned above, some seem to be associated with colonic stasis, and others have no demonstrable cause.

Grossly, there may be nothing notable or the nerves may be hyperemic and swollen. The peripheral parts are more severely affected than the radicular. Microscopically, there is marked degeneration of the myelin sheaths. The axis cylinders often escape but may show granular degeneration, varicosity and fibrillation. There is proliferation of the sheath cells and infiltration of large and small mononuclear cells, some of which are phagocytic. Healing takes place with some fibrosis, restoration of myelin sheath and regeneration of axis cylinders.

Infectious Granulomata. Tuberculosis.—Tubercle bacilli gain entrance to the central nervous system through the blood stream or by direct extension of tuberculosis from neighboring lesions, particularly those in bones such as the ear region of the parietal bone or the vertebræ. Lymphatic transmission probably occurs, especially from perirenal tuberculosis and retropharyngeal tuberculosis.

Tuberculous inflammation of the cerebral meninges is almost invariably hematogenous, and the point from which the disease is disseminated may be anywhere in the body. The lesion is most frequent in childhood and often traced to tuberculous mediastinal lymph nodes, pulmonary tuberculosis, tuberculous cervical lymph nodes, retropharyngeal tuberculous abscess, tuberculosis of bones and other sites. In our experience tuberculous cerebral meningitis in adults is usually secondary to pulmonary tuberculosis, but may be secondary to tuberculosis elsewhere, especially the urogenital system and bones. The lesion is usually at the base of the brain, covers brain stem and extends forward to the optic commissure. Owing to the loose arrangement of pia-arachnoid, it tends to spread. Thus, it passes laterally in the Sylvian fissures, also over the upper surface of the cerebellum and into the great longitudinal fissure, sometimes along the olfactory bulbs, downward into the spinal canal, and may ultimately be generalized over the entire brain. Not infrequently, it extends into the ventricles. The lesion affects the pia-arachnoid but, as a rule, affects the dura only when bony involvement is present. In some of the earlier cases the lesion is a miliary tuberculosis of the meninges, hidden in the sulci and fissures and more clearly visible when the pia is stripped and held up to the light. Usually, however, in the fresh specimen the tubercles are clearly visible. Frequently, there is in these cases a small amount of fibrinous exudate which may merely cloud the membranes or may be easily seen. Fibrinous exudate may

be prominent and the tubercles hard to find. The exudate sometimes becomes purulent. In some cases the process extends a short distance into the brain substance to produce a tuberculous meningo-encephalitis. Microscopically, the lesion may be predominantly an acute inflammation. Tubercles identify it, as a rule, but sometimes only focal areas of necrosis give the clue. Special stains usually show numerous tubercle bacilli.

Tuberculous spinal meningitis is often found in the upper parts of the cord as a result of extension from cerebral meningitis. A most important form is that due to tuberculosis of the vertebræ. This may result in a subacute or chronic tuberculous pachymeningitis, usually localized, conglomerate, and

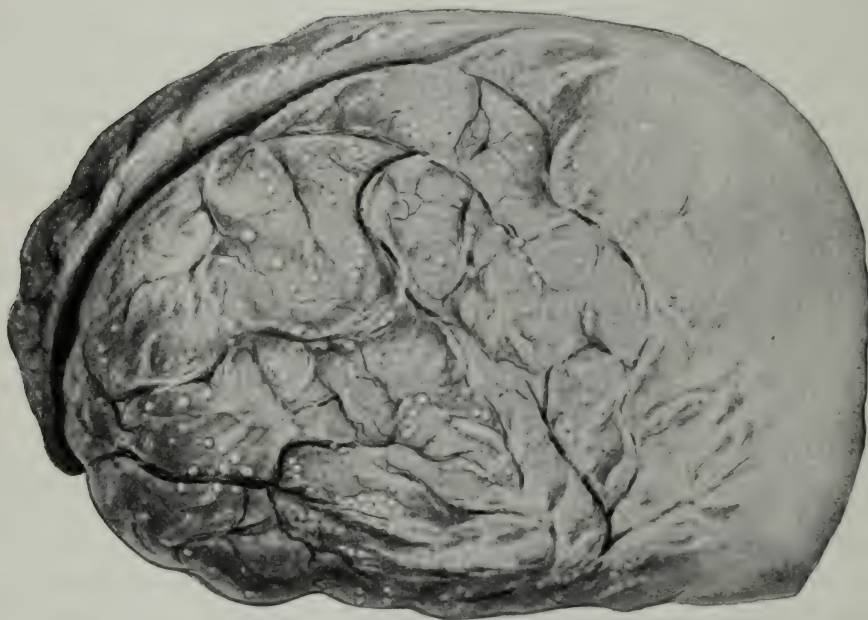


FIG. 421—Miliary tubercles in pia-arachnoid of the cerebrum.

sometimes so massive as to produce pressure. The more acute forms invade also the pia-arachnoid and may remain local or extend along the cord, even to the brain. This may be a miliary tuberculosis with little acute inflammation, or may be an acute fibrinous tuberculous inflammation, or may become purulent. Tuberculous meningitis of the cord, especially near bone lesions from which it takes origin, is more likely to involve nerve substance than is tuberculous cerebral meningitis. This tuberculous meningomyelitis may become a complete transverse myelitis.

The ependyma of the ventricles may be involved as a result of extension from meningitis or occasionally may be attacked without involvement of the meninges. The lesion may be miliary tuberculosis or a fibrinous or purulent inflammation. Interference with drainage may produce internal hydrocephalus. This may be due to the exudate, or may result from large tuberculous

masses in cerebellum or brain stem. In the former case the fluid contains exudate; in the latter it is usually clear.

Tuberculosis of the brain is usually a conglomerate lesion, commonly solitary but sometimes multiple. It is much more frequent in childhood and adolescence than in later life. It occurs especially in the brain stem and cerebellum, and when it involves the cerebellum is usually in the cortex. The bacilli evidently lodge in a small blood vessel immediately under the meninges and produce a small tubercle which enlarges by the formation of daughter tubercles. Even in tubercles with a diameter of a centimeter or more, daughter tubercles are to be found, but sometimes the lesion seems to become quiescent and daughter tubercles, fusing with the parent mass, are no longer present as such. Grossly, the mass is well defined, with slight or no marginal hyperemia, but sometimes with a surrounding zone of softening of the nervous substance. The firm caseous mass, sometimes gelatinous to gross inspection, only rarely undergoes softening or liquefaction. Histologically, the margins show the characteristic cell forms, and if daughter tubercles be present the diagnosis is easily established. Usually in older lesions the tubercle bacilli cannot be demonstrated microscopically, and the final diagnosis is made by exclusion or by animal inoculation. As such tubercles reach the surface they may incite a local or more diffuse tuberculous meningitis. Interference, by pressure, with drainage from the ventricles causes an internal hydrocephalus.

Disseminated miliary tuberculosis of the spinal cord is rare. A solitary conglomerate tubercle has much the same appearance as in the brain, but is less common in the cord. Secondary tract degenerations may be prominent. Such a tubercle may be metastatic or result from direct extension of lesions of meninges or vertebræ. Extensive disease of the vertebræ may lead merely to compression of the cord or to a tuberculous transverse myelitis. Tuberculous spinal meningitis may be secondary to tuberculosis within the cord.

Peripheral nerves may be involved and destroyed in tuberculous foci. Sometimes tuberculous meningitis may involve cranial and spinal nerves as they pass through the meninges and lead to degeneration beyond the lesion.

Syphilis.—This disease may affect the nervous system in many ways, including subacute inflammations of the meninges, gumma formation, vascular lesions and the progressive glial overgrowths and degenerations of tabes dorsalis and general paralysis of the insane. Certain investigators (Nichols, also Marie and Levaditi) present evidence to support the view that certain strains of the *treponema pallidum* have special affinity for the nervous system, but this has yet to be finally established. Lesions may appear fairly soon after the chancre and there is little doubt that in the septicemic period the nervous system is infiltrated with *treponemata*. Other lesions may not occur for many years after the chancre. Diseases such as general paralysis of the insane and tabes dorsalis were formerly regarded as parasymphilitic and due to indirect effects of the *treponema*, but the demonstration of *treponema* in the brains of general paralysis (Noguchi), even though the organism has not been found in tabetic cords, gives rise to the modern view that these lesions represent a phase

in the cyclic manifestations of syphilis. Of further interest is the fact that the Wassermann test may be positive in the spinal fluid of neurosyphilis but negative in the blood.

Congenital syphilis may manifest itself in gummatous and non-gummatous meningitis, gummata in various parts of the central nervous system, areas of softening and atrophic changes. It is considered possible that various developmental defects, various paralyses of infancy, areas of softening and porencephaly are due to congenital syphilis.

Gumma may occur in any part of the central nervous system and peripheral nerves. The gumma of these regions has the same characters as elsewhere. It originates either in meninges or nerve sheaths or in the adventitia of blood vessels. In the brain and cord it is most often superficial but penetrates into the nervous substance and may induce severe symptoms. As contrasted with tubercle, it occurs more often in adult life than in childhood, is more super-

ficial, more irregular in outline, has a broader surrounding zone of fibrous growth, often hyperemic and sometimes hemorrhagic, and is less likely to caseate. The neighboring meninges may show subacute or chronic inflammation and the surrounding nerve substance may show edema, encephalitis or myelitis. The symptoms depend upon the site of the lesion.

Meningitis, in order to be identified histologically, must be a gummatous meningitis. Neverthe-

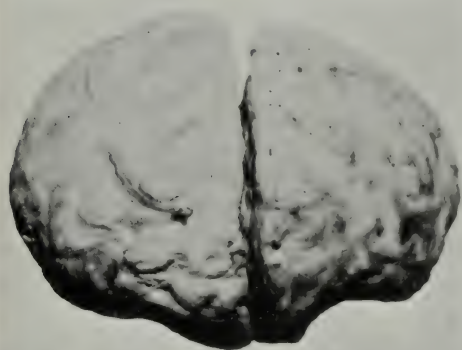


FIG. 422.—Chronic leptomeningitis of syphilitic origin. Note opacity of the thickened meninges.

less, a non-gummatous form is described, which while not histologically characteristic, seems to be due to syphilis. If gummatous meningitis affect the pia-arachnoid alone, it is usually confined to the base. The membrane is thickened, sometimes edematous and exhibits small white plaques. More frequently, however, the soft meninges and dura are involved together, especially over the vertex, but sometimes extending over the entire cerebral surface so as to form a thick, dense, opaque sheet adherent to skull and brain. A similar condition may occur in the cord. This accounts for some of the cases of chronic cervical pachymeningitis described above, but most of such cases are not syphilitic. The lesion of syphilitic meningitis is essentially a gummatous granulation tissue. The tissues are infiltrated with cells of lymphoid type but, as the process gets older, large mononuclears may predominate. Small gumma-like foci occur and often show necrosis. These may organize to form fibrous plaques. Fibroblastic proliferation, principally from the vascular adventitia, ultimately produces the dense thickening of the meninges. The blood vessels are frequently involved in one or other form of syphilitic vasculitis. The underlying brain or cord substance often shows

degeneration of the parenchyma, with intact or proliferated glia. The nerves, especially the cranial nerves, the oculomotor, abducens and optic, may become involved in an interstitial or gummatous neuritis.

Krause describes non-gummatous syphilitic meningitis as involving particularly the soft meninges in the form of thickening and opacity. There is first a perivascular infiltration of lymphoid cells and a few plasma cells, especially around the veins, which becomes more and more diffuse. Fibrosis proceeds from the adventitial cells and may become dense, but usually the cellular infiltration, although decreased, remains in evidence.

Syphilitic arteritis only rarely occurs independently of a syphilitic meningitis. Most cases are therefore meningo-arteritis. Although Huebner in his classical description regarded the lesion as an endarteritis, the present view is that it is primarily adventitial. It is probably due to the presence of treponemata in the perivascular lymphatics which may inaugurate a gummatous granulation or perhaps merely a fibrosis. This involves not only the adventitia but gradually extends into the media, with atrophy and disappearance of muscle. The elastica may show multiple laminae, but this is probably due to splitting rather than multiplication. The intima then takes part in the fibrosis and becomes thickened. Grossly, the vessels are thick and inelastic and may show minute gray perivascular nodules. Where vasa vasorum are present, they may be occluded by the disease and the artery may rupture. The advance of the fibrosis may so weaken the wall that aneurysm may form and subsequently rupture. The gradual reduction of the lumen by the intimal thickening may cause atrophy of the area supplied. The vessel may become obliterated with consequent encephalomalacia or myelomalacia, either by advance of the intimal thickening or by thrombosis. Apoplexy and hemiplegia in middle life may be due to syphilitic arteritis, either because of occlusion or rupture, but a similar accident at this period may also be due to a hypertension the result of diffuse non-syphilitic arteriocapillary disease. Syphilitic arterial disease as it affects smaller arteries in the brain substance may produce irregularly distributed small areas of encephalomalacia.

According to Buzzard and Greenfield, syphilis is the most common cause of *myelitis*, which as a rule, takes the form of a meningomyelitis of transverse form. The cervical region is usually affected. The meninges are thickened and adherent. The soft meninges are infiltrated with small round cells and show changes in the blood vessels. The vascular lesions of meninges and cord may be only perivascular infiltration by small lymphoid cells with no alteration of the vessel lumen. With only moderate perivascular infiltration there may be marked dilatation, presumably paralytic, and thrombosis of the finer vessels. There may also be the syphilitic arteritis described above. As a result of the vascular lesions, and perhaps also due to the effects of products of the treponema, degeneration occurs in the nerve cells and fibers. Scavenger cells may be numerous. The glia may be well preserved and ultimately proliferates to constitute most of the scar. The infiltration may take on the characters of gummatous granulation and obvious gumma formation is not rare.

General Paralysis of the Insane.—This disease, common in the fourth and fifth decades, but also occurring in juvenile form as the result of congenital syphilis, is called progressive paralysis of the insane, dementia paralytica, and paresis. History of syphilis, positive blood and spinal fluid Wassermann tests in a large percentage of the cases, indicate its syphilitic nature, and the demonstration of living treponemata in the brain substance (Wile) shows that it is due directly to invasion by the organisms. Manonelian states that the treponemata appear first in the meninges, enter the brain through lymphatics and then attack the ganglion cells. Grossly, the skull bones may be thick and dense, the dura may be fibrous and adherent, chronic internal hemorrhagic pachymeningitis is common, and the leptomeninges are often thick and opaque,

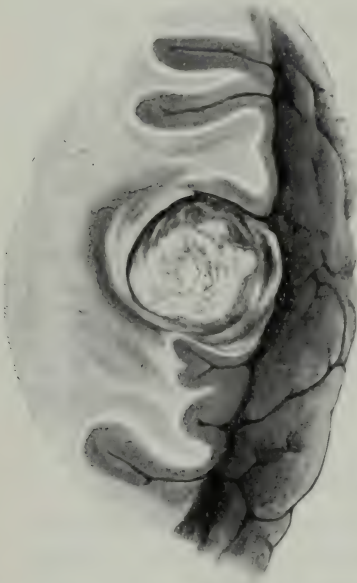


FIG. 423—Gumma of cerebral cortex.

especially over the frontoparietal region. Fluid, sometimes cloudy, may be in excess in the meninges and the ventricles, and the ependyma of the latter is often the seat of hyperplasia and slight roughening. Except in early cases, the brain is reduced in size and weight, a change due especially to involvement of the cerebrum. The white matter may be soft and edematous. The gyri are reduced in size, especially in the frontoparietal region, and the sulci wide. Cross section shows thinning of the cortical gray matter and prominent blood vessels. The cord may show grossly visible degeneration of the descending tracts. Obvious syphilitic meningitis, myelitis and gumma formation may be found.

Microscopically, the cortex shows perivascular infiltration of lymphoid and plasma cells, dilatation of vessels and sometimes new capillaries. Neuroglia proliferation is prominent and many astrocytes are found. Rod

cells may be numerous but scavenger cells are rare. The cortical nerve cells are in disorderly arrangement and cellular degeneration, going on to complete destruction, is observed, which affects especially the pyramidal cells. Neuron degeneration affects particularly the association fibers of the brain and the pyramidal tracts of brain, brain stem and cord. Cells of the ventral horns of the cord, of the dorsal root ganglia, and even the Purkinje cells of the cerebellum may show slight degeneration in the form of chromatolysis. Disease of the posterior columns, like that of tabes, may be associated.

Tabes dorsalis, or locomotor ataxia, is a disease of middle and later life, which, like dementia paretica, attacks males more often than females. Many cases give a history of syphilis and the Wassermann test of blood and spinal fluid is positive in nearly all cases. It can now be stated with assurance that

tabes is due to syphilis, although spirochetes are not demonstrably associated with the lesion as in general paralysis.

Grossly, in the advanced lesion, the posterior columns are shrunk and on cross section are of pale gray color and retracted. Reduction in size of the posterior roots of the spinal nerves within the dura and sometimes of the optic nerve may be detected. The soft meninges on the dorsal surface of the cord may be thickened.

Microscopically, the posterior root ganglia may be the seat of slight fibrosis but the cells are normal. The peripheral neurons may be the seat of slight atrophy. The central neurons are the seat of degeneration with disintegration and loss of myelin and destruction of axis cylinders. This change affects the nerves as they pass into the cord but is primary in the posterior roots. Thus, the short fibers which pass directly to the dorsal horns are affected. So also are the medium fibers, which pass upward to enter the column of Clark.

The long fibers, similarly affected, pass upward to the nuclei gracilis and cuneatus, gradually assuming a position toward the septum to constitute the column of Goll. Thus, depending upon the level examined, the columns of Burdach and Goll may be variously affected. The lesion usually begins in the lumbar regions and shows changes as it ascends. If, however, thoracic roots are affected, the change in the upper cord is

more extensive. Associated with the degeneration there is a gliosis, the fibrous septa are increased in bulk and the blood vessel walls become thick and hyaline. The posterior horns and the column of Clark may be reduced in size by the destruction of the entering fibers. The intersegmental association fibers are usually not affected. The tract of Lissauer, being made up of descending radicals of the entering fibers is usually degenerated. The optic nerve is sometimes the seat of degeneration which begins near the eye and extends toward the commissure. The trigeminal and glossopharyngeal are sometimes affected and accordingly the trigeminal root fibers and those of the fasciculus solitarius in the medulla degenerate and disappear. As with general paralysis, more distinctive syphilitic lesions, such as syphilitic meningitis, vascular lesions and gumma, may occur.

The loss of sensation, the ataxic gait, the failure of coordination, the decreased reflexes, all can be attributed to the fault in the sensory system. Visceral pains and perhaps the Argyll-Robertson pupil may possibly be due to lesions of the sympathetic system, but this association is by no means clearly established.

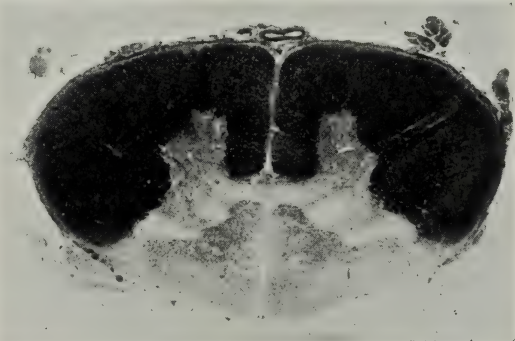


FIG. 424—Cross section of cord showing degeneration of posterior columns in tabes dorsalis. Weigert-Pal. Microtessar 32 mm. Courtesy of Stanley Cobb, M.D.

Leprosy affects especially the peripheral sensory nerves in the form of a chronic inflammation of the connective tissues, which subsequently leads to degeneration and destruction of the axis cylinders. Bacilli may be found in the lesions. Only rarely do the bacilli penetrate to the spinal ganglia and cord. Occasionally, the posterior columns show degeneration. Cutaneous nerves may be involved in lepra nodules. According to Monrad-Krohn, there is no histologic difference between the nerve lesion of the maculo-anesthetic and nodular forms of the disease.

Actinomycosis may penetrate the brain or cord from bone lesions or perhaps the organisms may be transported to brain or spinal nerves by the blood stream. This disease, however, is rare (see Howard).

Special Infectious Diseases.—In addition to those infectious diseases whose manifestations are inflammatory, such as epidemic encephalitis, acute poliomyelitis and the infectious granulomata, certain others require discussion, especially tetanus, herpes, chorea, rabies and trypanosomiasis.

Tetanus.—This disease is due to the toxin of bacillus tetani. The bacteriology is well presented by Fildes and the immunology in text-books on immunity. The organisms are found in soil contaminated by horse manure and in the intestine of the horse. They may also be found in the intestine of man, and such carriers have antitoxin in the blood (TenBroeck and Bauer). The organisms or their spores are only effective in wounds of such character as to permit anaërobic growth. Injury of tissue by trauma or by pyogenic infection also seems necessary. Although other investigators maintain that the toxin manufactured in the wound is transferred to the nervous system by the blood, Teale and Embleton find that it ascends to the central nervous system by way of the neural lymphatics and axis cylinders, and cannot pass from the blood capillaries to the central nervous system. The incubation period is variable but usually is about eight days. In man, as a rule, the first symptom to appear is trismus of the jaw muscles, but in experimental animals, when the toxin has been given subcutaneously or intramuscularly, the first spasms are near the injection site. There follows a period of excitable reflexes, clonic and then tonic spasms, more and more widespread, terminating in death.

The pathological anatomy of tetanus has no features to distinguish it from infectious disease in general. Petechiæ may be found in muscles and other places. An interstitial neuritis may occur but it is not specific. Getsowa describes chromatolysis of the cells of the spinal cord, especially in Clark's column, but Barros points out that such changes occur only after postmortem autolysis sets in, and may similarly follow other spasmogenic agents such as strychnine and picrotoxin. The sympathetic ganglia may show cellular degenerations, like those seen in many other infections (Mogilnizky). Aschoff and Reinhold found that the majority of tetanus victims die of cardiac failure (partly due to toxemia and partly to asphyxia), many die of bronchopneumonia and a few of secondary infection. Spiegel found petechiæ and Zenker's necrosis of muscle, presumably due to asphyxia.

Herpes.—The external manifestation of herpes is the appearance of an

erythema, followed by a multilocular vesicular eruption, which encrusts and the crusts drop off. Herpes febrilis simplex usually occurs on the face and ordinarily leaves no scar. It accompanies a variety of acute infectious diseases, is frequent following the common cold, or may be spontaneous. Herpes genitalis follows irritation about glans penis or labia. Herpes cornealis resembles herpes febrilis except as to situation. Herpes zoster is most frequent on the trunk but may occur over the course of any cutaneous sensory nerves. It is unilateral, often leaves shallow scars and apparently produces a local immunity in the area affected.

The forms of herpes, other than zoster, are due to a virus the exact nature of which has not been finally established. The organisms are extremely minute and probably, but not certainly, filterable. The virus is transmissible to rabbits, survives through many generations and has been reinoculated successfully in man. The cornea is the favorite seat of experimental inoculation, but as Goodpasture and Teague have shown, many other tissues are susceptible. There is apparently some difference in tissue affinity of strains, some of which seem to be strikingly neurotropic. Peripheral inoculation in rabbits is often followed by an acute myelitis. Direct and peripheral inoculations may produce an encephalitis which histologically closely resembles epidemic encephalitis (see DaFano). The virus travels to the central nervous system along the course of peripheral nerves (Goodpasture). In the human and experimental lesions, peculiar inclusions are found in the cell nuclei, and in addition minute globular bodies, more widely distributed. Similar intranuclear bodies may be found in varicella and other conditions (see Von Glahn and Pappenheimer). Whether these bodies are in some way directly related to the virus or are secondary degenerations is not established. The similarity of the virus of herpes to that of epidemic encephalitis is striking but the two are probably distinct.

Although Teague and Goodpasture produced experimental lesions similar to those of human zoster, by using virus from a patient with doubtful zoster, Cole and Kuttner were unable to identify a transmissible virus in genuine human herpes zoster. Netter and Urbain claim to have obtained a virus from zoster which shows cross reactions immunologically with that of varicella. It cannot be said that a virus of herpes zoster has as yet been conclusively demonstrated.

Although ganglion lesions may be observed in herpes simplex (Howard) they are practically constant in zoster. In the usual case of herpes zoster the ganglion affected is a posterior root ganglion of the thoracic region. It is swollen, soft and hyperemic. Microscopically, there are hyperemia, sometimes with small areas of hemorrhage, edema, and infiltration by lymphoid cells, especially around the capillaries. The nerve cells are variously affected. Some are destroyed and others are normal. Some are swollen and stain diffusely but do not show chromatolysis (Buzzard and Greenfield). Some show invasion by mononuclear cells, neuronophagy. The inflammation may extend into nerve or dorsal root (Holmes). As a result of destruction of cells, degeneration

affects the nerve fibers and may extend through the roots into the cord. Healing results in cicatrization, sometimes with cyst formation. The lesion in the ganglion is of much the same nature as that observed in other parts of the central nervous system in epidemic encephalitis and acute poliomyelitis.

Herpes zoster may also be secondary to organic diseases of the cord such as tabes, to disease of the vertebræ such as tuberculosis and tumor, or to severe trauma of the spine. This is due to involvement of the spinal root ganglion and is etiologically different from the so-called idiopathic form discussed above.

Chorea.—This disease, often called Sydenham's chorea, occurs principally in children but may attack adults, affects females more often than males and is rare in races other than whites. It is characterized by irregular purposeless movements and may exhibit psychic manifestations, but it is not often fatal. It is not infrequently associated with rheumatic fever, with acute endocarditis, and may occur in the early months of pregnancy. Its association with rheumatism and endocarditis strongly suggests its infectious origin. Various organisms have been isolated, but we agree with McCarthy that "the exact bacterial cause of the disease has not been conclusively proved."

Examinations of the central nervous system have shown hyperemia, minute hemorrhages, thrombi in small blood vessels, small areas of necrosis and sometimes inflammatory exudate, especially in the basal ganglia (Castren). The changes are by no means constant, are not characteristic and do not explain the symptoms.

Rabies.—This is an acute specific infectious disease to which practically all mammals are susceptible and to which birds and reptiles seem resistant. The virus acts principally upon the central nervous system and is excreted especially through the salivary glands. It is transmitted by bites or by contamination of open wounds by infected saliva. Laboratory infections in man are rare, and it is possible that the saliva exercises some function, other than carriage of the virus, in establishing the infection. The virus seems to travel by way of the axis cylinders (Goodpasture), and bites upon head and face are followed by a shorter incubation period than those upon the extremities. The average incubation is about seventy-two days but may vary from nineteen days to more than a year. After prodromal symptoms there is spasm of muscles of deglutition, followed by hyperexcitability, convulsions and death either from asphyxia or exhaustion (see Keirle).

It has been thought that the cause of the disease is a sporozoon parasite (see Watson) named by Calkins *neurotrichytes hydrophobiæ*. It was supposed that the Negri bodies, found in the nerve cells of brain cord and ganglia, especially frequent in the hippocampus major and in the Purkinje cells of the cerebellum, represent a stage in the cycle of the parasite. The Negri bodies are round, stellate or spindle form, with acidophilic cytoplasm, and contain both fine basophilic granules and a nucleus-like basophilic central body. Other similar bodies, "lyssa bodies" are found which contain no central basophilic substance. The studies of Goodpasture indicate that the acidophilic substance

is a fused mass of degenerate intracellular neurofibrils and the nucleus-like mass is made up of retrogressive products of mitochondria. Although this change is almost certainly due to activity of the virus, the Negri and lyssa bodies are probably not parasites. Noguchi has cultivated a filter passing virus, appearing in culture as minute globular and pleomorphic chromatoid bodies. Upon inoculation the filtrate produces rabies.

The gross examination of the central nervous system usually shows no change, except sometimes hyperemia and minute hemorrhages. Microscopically, there is perivascular infiltration of lymphoid cells. The affected nerve cells show degeneration and the dendrites may be swollen and granular. They may be surrounded by a rim of neuronophages, phagocytic glia cells. The Negri bodies are usually intracellular but may be extracellular. The neuroglia may show proliferation. These lesions are especially prominent in the medulla but may be much more widespread. The ganglia, including the Gasserian, plexiform and spinal, are usually the seat of a subacute inflammation with

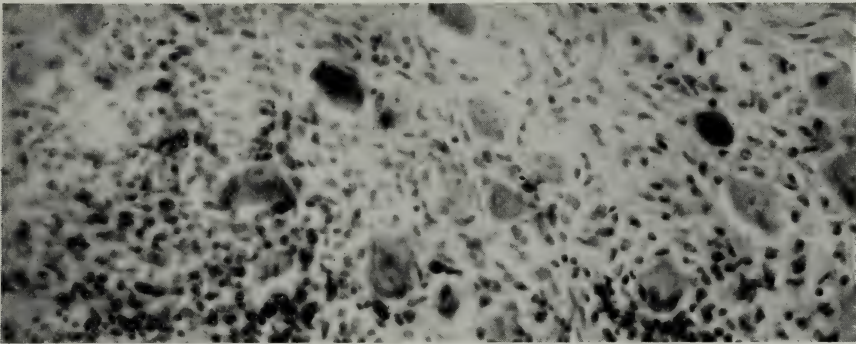


FIG. 425—Gasserian ganglion of rabies, showing marked lymphoid cell infiltration, and in lower right hand corner, neuronophagia.

proliferation of endothelial cells of the capsule and infiltration between the ganglion cells. The latter undergo degeneration and neuronophagy. This is apparently constant in the disease but not positively diagnostic, since it may be found in other conditions (Frothingham). Peripheral nerves from the site of infection may show degeneration as also may the fibers associated with the ganglia. The salivary glands may show acute inflammation.

Trypanosomiasis.—In African sleeping sickness, caused by *trypanosoma gambiense* and *trypanosoma rhodiense*, the brain and cord show thickening and often adhesion of pia-arachnoid. Slight or moderate hydrocephalus may occur and the cerebrospinal fluid may be yellow. There is extensive lymphoid infiltration of the pia-arachnoid and perivascular spaces. The cerebral cortex may show degeneration of the pyramidal cells and the cord may show diffuse sclerosis.

In Chagas' disease, an infectious disease seen especially in South America due to the *trypanosoma cruzi*, the acute form may show marked involvement of the central nervous system. There may be acute inflammation of both cerebral and spinal meninges. In regions of the cord, in relation

to lodgment of the parasites, there are areas of marked degeneration of cells and fibers (Chagas).

Diseases of Obscure Origin.—There are certain diseases of the central nervous system whose exciting cause is unknown, and which therefore cannot be classified in the groups which have been discussed. The description of these is given in the following paragraphs.

Amyotrophic Lateral Sclerosis.—This is a disease of middle life characterized by degeneration of the motor neurons and atrophy of voluntary muscles. Although syphilis may produce similar effects and lead poisoning seems to be associated with certain cases, the disease cannot be ascribed to any definite cause. It appears to be primarily a degeneration of motor neurons, peripheral and central, perhaps based upon some inherent susceptibility or abiotrophy of these systems. Clinically, the usual case shows spastic paraplegia or tetraplegia followed by muscular atrophy. The bulbar type begins in the nerves and muscles supplied from the medulla and may progress to the extremities. The amyotrophic type shows prominence of the muscular atrophy and slight nervous symptoms. In the spastic type, the spasticity is marked and the atrophy delayed.

Grossly, it may be possible to see reduction in size of the ventrolateral columns of the cord and precentral convolutions of the brain. Microscopically, there is degeneration of nerve fibers and their medullary sheaths, and degeneration of cells with chromatolysis, displacement of nuclei, and sometimes increase of pigment, which is followed by a state of atrophy or complete disappearance. Reactive overgrowth of neuroglia is slight. The nerve degeneration is observed most markedly in the cord, affecting the ventrolateral columns. The sensory columns remain free except that occasionally the upper parts of the column of Goll may show slight sclerosis. The motor columns are often not uniformly affected, some fibers being in a state of more advanced degeneration than others. The lesion affects the ventral roots and peripheral nerves. The cells of the anterior horns show varying degrees of degeneration and pigmentation. The nerve degeneration ascends, usually equally on both sides, to various levels of the cord, to the medulla, to the pons, sometimes to the internal capsule and even to the cortex, occasionally with involvement also of the corpus callosum. The cortical cells of the precentral and sometimes postcentral areas show degeneration. The medulla may be involved in varying degree. The nerve degeneration affects both intra- and extrabulbar parts. The ganglion cells are degenerated and may disappear, especially in the hypoglossal nucleus. The motor nucleus of the trigeminus and the nucleus ambiguus are often affected. The facial, glossopharyngeal, spinal accessory, and other nuclei may also suffer.

The skeletal muscles and, when the bulb is involved, the tongue, show wasting without fat replacement. Microscopically, the atrophy is seen to affect irregularly disposed groups of fibers, which are of decreased diameter but with preserved transverse striations. The atrophy may be complete, leaving only bands of proliferated sarcolemma nuclei. Replacement fibrosis may be marked.

Landry's Paralysis.—Certain features indicate that this disease is infectious in origin and Buzzard and others have recovered pathogenic bacteria. For the present, however, its infectious nature is not clearly proven and its origin is still obscure. It occurs usually in the third and fourth decades of life, attacks males principally, and is characterized by a progressive flaccid paralysis without atrophy or changes in electrical response of muscles. Some cases of poliomyelitis and of multiple neuritis present a confusing clinical picture. The spleen and lymph nodes may be enlarged, but otherwise there are no gross morbid changes save for hyperemia of the gray matter of the cord. Microscopically, some of the cells of the gray matter, more especially those of Clark's column, show chromatolysis and displacement of the nucleus. The myelin sheaths of the cord and sometimes of the peripheral nerves may show small areas of fatty change, but not the diffuse change of Wallerian degeneration. The vessels may be hyperemic and rarely show slight perivascular round cell infiltration. The neuroglia shows no changes except an occasional swollen cell.

Subacute Combined Degeneration of the Spinal Cord.—This

is often referred to as a sclerosis, but since glia production is relatively slight, the term is not justified. Combined lesions of motor and sensory paths may occur in connection with other disease, as general paralysis of the insane.

Subacute combined degeneration occurs principally in the fourth and fifth decades, and about

equally in both sexes. Starting as a mild spastic or ataxic paraplegia, it may progress through a stage of complete spastic paraplegia to one of flaccid paraplegia. Sometimes it appears to follow or complicate syphilis, or other chronic infection. It is not infrequently associated with high grade anemias of secondary or of primary type. There has been much discussion of the relationship of anemias, but the present view favors the conception that the agent which causes the cord lesion is also responsible for the anemia.

Except for occasional cases with slight atrophy of the frontoparietal lobes of the brain, the gross examination of the central nervous system is usually negative. Microscopically, the principal lesions are foci of necrosis and degeneration in sensory and motor tracts. The necrosis is usually most marked in the mid-thoracic region, sometimes with complete destruction of all the white matter except a few fibers near the gray matter. The long tracts are affected first, as a rule, with degeneration of sensory tracts above and motor tracts below the mid-thoracic segments. The posterior tracts are usually more severely affected, but ultimately the degenerations may be extensive and involve both



FIG. 426.—Cross section of cord in subacute combined degeneration, showing degeneration of posterior and posterolateral columns. Weigert-Pal. Microtessar 32 mm. Courtesy of Stanley Cobb, M.D.

exogenous and endogenous fibers. Chromatolysis is sometimes seen in cells of the column of Clark and the pyramidal cells of the cerebral cortex. Vascular changes are slight or absent. The lesion is probably not inflammatory and reactive gliosis is slight. Although the necrosis is probably, but not certainly primary, it is thought to be toxic rather than vascular in origin.

Multiple Sclerosis.—This disease, also called disseminated sclerosis, insular sclerosis and *sclerose en plaque*, is of common occurrence, begins in early adult life and seems to attack both sexes about equally. It is a progressive disease, with periods of remission of symptoms. Easy fatigue and weakness may be followed by paralyses, tremors, ataxia, spasticity; disturbances of speech, vision, hearing and mental changes. Symptoms may appear abruptly, regress or disappear, and after recurrences, become permanent.

Fundamentally, the disease is characterized by the appearance of numerous areas of myelin degeneration and gliosis, scattered irregularly throughout the central nervous system. It is apparently degenerative and inflammatory.

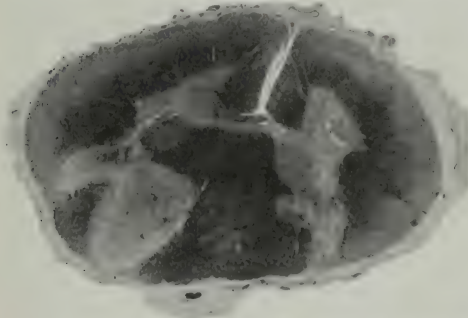


FIG. 427.—Cross section of cord of multiple sclerosis, showing an area of sclerosis in left posterior columns—not a tract degeneration. Weigert-Pal. Microtessar 32 mm. Courtesy of Stanley Cobb, M.D.

Cerebrospinal syphilis may resemble it, but is not the cause, and no other definite cause can now be given. Inconclusive reports point to its transmissibility to animals and suggest that a spirochete may be the responsible organism, but the work of Collins and Noguchi gave negative results. There is a certain familial incidence which suggests that it may be hereditary.

Gross inspection may disclose more or less firm, translucent gray patches irregular in outline and varying in size from a millimeter or less to several centimeters. Patches may be found in any part of the cord, the pons, the medulla, the basal ganglia and even in the cerebral cortex, but only rarely in the cerebellum. Histogenetically, the lesion seems to originate in degeneration of the medullary sheaths, and this is followed by reaction on the part of the neuroglia and of the mesoblastic tissues. In the earlier lesions the lipoidal debris of the myelin is readily shown, but later it disappears. The axis cylinders may be unaltered or may show varicose swelling and subsequently, as gliosis progresses, may disappear. Tract degenerations, however, are irregular and changes in the ganglion cells hard to find. The neuroglia shows well marked fibrillar proliferation. Myelin detritus is found free and in many scavenger cells of glial origin and probably of mesoblastic origin. Some of these have been called myeloclasts and myelophages, which are probably merely large scavenger cells. The phagocytic cells may accumulate in large numbers in perivascular spaces. As to the mesoblastic changes, the pia-arachnoid is often the seat of fibrous hyperplasia and diffuse infiltration by small mononuclear cells and by phagocytes. The same change may be found in the fibrous septa. The blood

vessels may be normal, or may show fibrosis or hyalinization of the walls. The perivascular spaces may be free, or may be infiltrated by small and large mononuclears, or by phagocytes. The choroid plexus may show vascular changes and the covering cells may contain fatty droplets. The student is referred especially to the volume on multiple sclerosis, of the Association for Research in Nervous and Mental Diseases, Hoeber, New York, 1922.

Syringomyelia.—Although many cases of syringomyelia represent a tumor-like growth, certain others are not of this nature and for that reason the disease is discussed here instead of under the heading of tumors. It is a disease of early adult life, but may occur in infancy, and affects both sexes about equally. Clinically, there are dissociated anesthesia in which pain and temperature sense are affected without loss of tactile sense, progressive muscular atrophy with twitchings, and trophic and vasomotor disturbances. The bones may be atrophic and disposed to fractures; the joints may be the seat of arthropathies like those of tabes. The lesion is a cavitation extending along the center of the cord; rarely it affects the medulla and then bulbar symptoms occur.

Grossly, the central cavitation may be so small as to be detected only on transverse section, but it may be so large that the cord is like a tube whose lumen may show irregularity in its calibre. Usually, the cavitation is more marked in the cervical and upper thoracic cord. The cavity may be central or somewhat lateral, and in outline

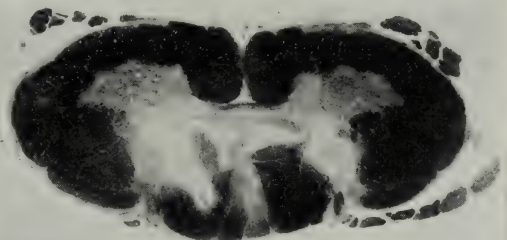


FIG. 428—Cross section of cord of syringomyelia, showing irregular, generally central, cavitation. Weigert-Pal. Microtessar 32 mm. Courtesy of Stanley Cobb, M.D.

circular, oval or irregularly stellate. The contents may be limpid or gelatinous, colorless or some shade of yellow or brown. Microscopically, the cavity may be in connection with the central canal or if, as is usual, it be separate, it is likely to be posterior to the canal. Thus, the gray commissure is practically always interrupted. The inner margin may be partly or completely lined by ependyma, may be a smooth surface of glia, or a rough necrotic surface. Surrounding this is an overgrowth of fibrillar neuroglia of variable density and thickness. The glial growth progresses both by invasion and compression of the surrounding substances. It varies in vascularity, and small hemorrhages or masses of blood pigment are not infrequent. The surrounding nerve tissue may be the seat of edema. The glial growth destroys and compresses parts of the horns and also leads to tract degenerations, especially in the pyramidal, ascending ventrolateral and dorsal tracts.

Because of the character of its vascular supply the central part of the cord seems to be a place of lowered resistance, and offers a path of progress for suppuration, hemorrhage and tumor growth. Some cases of syringomyelia seem to originate as the result of these lesions. The formation of the canal may be somewhat irregular and furthermore small islands of ependyma may be

found separated from the central canal. Hence, it is possible that hamartomatous displacement of medullar cells may ultimately lead to the blastomatous neuroglial growth of the usual case of syringomyelia.

It is likely that the dissociated anesthesia is due to interruption of the pain and temperature fibers of the gray commissure, whereas the tactile sense fibers ascend directly in the lateral and dorsal tracts and are less subject to interference. The paralyses are due to interruption of motor tracts. The muscular atrophy is due to lesion of the ventral horns. The other phenomena are as yet unexplained (Buzzard and Greenfield).

Paralysis Agitans.—This condition, also called shaking palsy and Parkinson's disease or syndrome, occurs most often in advanced middle life and affects males about twice as often as females. Clinically, it usually begins with tremor of head and upper extremities, with rigidity of muscles and mask-like face, followed by weakness affecting at first one extremity and then becoming more extensive.

Pathologically, the lesion is a degeneration of the fibers of the corpus striatum and of the cells of the pallidal system. Similar symptoms may be produced by such lesions in this situation as tumor, hemorrhage or encephalomalacia. The cord shows no significant changes. The muscles may be normal or may show areas of atrophy, swollen hyaloid fibers with diminished transverse striation and prominent longitudinal striation sometimes with splitting.

Tumors.—In the category of *brain tumors* are included all tumors which occur within the cranial cavity, even although some of them may originate in meninges, nerves, bones or other structures. They are somewhat more common in males than in females. Although they may be found at almost any age, Cushing states that more than half the tumors occur between twenty and forty years of age. This low age incidence is probably due to the fact that more than 40 per cent. of all intracranial tumors are gliomas. Although trauma may serve only to draw attention to the existence of a tumor, it is also likely that it may play some causative role. Brain tumors are malignant in effect by virtue of their position. Pathologically, some of them are not invasive and most of them show no disposition to metastasize.

The symptoms and signs are the result principally of local pressure or invasion, and of disturbance of the circulation of blood, lymph and cerebrospinal fluid. The brain is almost non-compressible and the skull resistant, so that increase in intracranial pressure is a most important phenomenon in brain tumors. The increases in pressure may be due to the bulk of the tumor, to edema around it, to obstruction to drainage of the great lymph sacs, and principally to obstruction of flow of cerebrospinal fluid. It varies, however, with the type of tumor growth, and some may be so invasive and destructive as not to lead to increased pressure. Situation is also important and the greatest pressures are produced by tumors of the posterior fossa. Multiple minute herniations of brain substance into the dura, particularly where local thinness is due to the presence of arachnoid villi, occur as the result of pressure (Franz). The increased brain volume may be seen in flattening of the convolutions and

in the formation of the so-called pressure cone on the inferior surface of the cerebellum, due to compression into the foramen magnum. There may be an osteoporotic pressure atrophy of the bones of the skull. The alleviation of such symptoms as headache, vertigo, drowsiness, vomiting, psychic disturbances, and alterations of respiration, circulation and temperature, by decompression craniotomy, makes it evident that these are due to increased pressure. The bulging optic disc, papilledema, or choked disc, revealed by ophthalmoscopic examination, is also due to the pressure. The cranial nerves tend to be pushed into their foramina, and this affects the optic nerve. Of further importance is the hypothesis that the condition is due also to com-

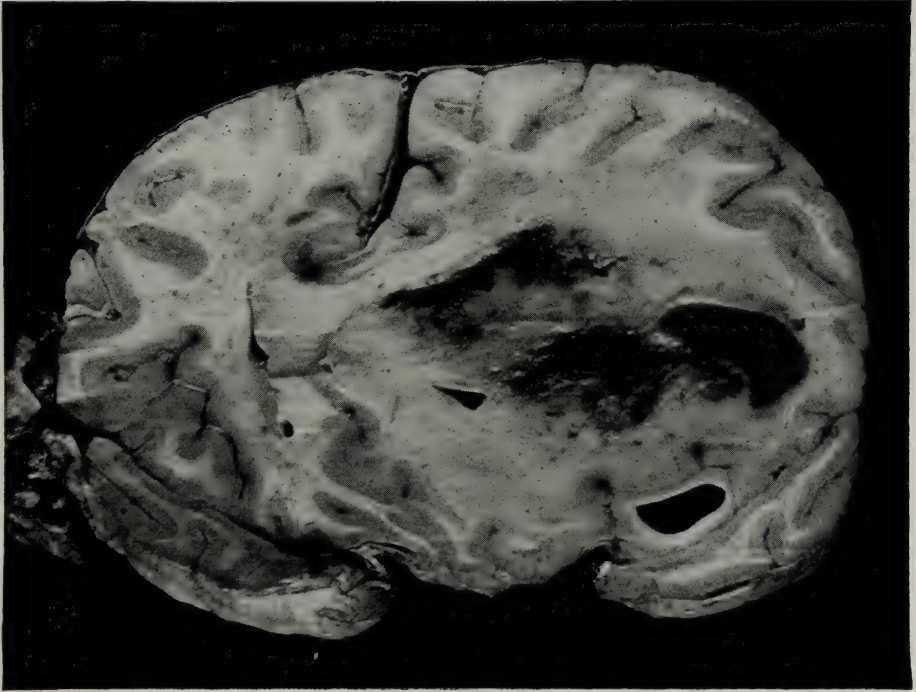


FIG. 429.—A large left frontal astroblastoma (Surg. No. 15031), extending backward through the major part of the hemisphere. The patient, aged twenty-seven, after four years of headaches with disturbance of vision, was admitted in coma, May 1921. The lesion was not localized and a right subtemporal decompression was performed. Readmission three months later, when a fatality occurred after a misdirected exploration. Note the presence of a small cyst, the evidence of recent extravasations and total absence of any peripheral demarcation of the lesion, even though relatively benign. (Two-thirds natural size.) A Classification of the Tumors of the Glioma Group, etc.

pression of the central vein as it crosses the optic sheath to enter the cavernous sinus. Convulsions may be due to general increase of pressure or to focal pressure or irritation. The focal manifestations of brain tumors are various, and the signs and symptoms are observed principally as disturbances of motor, sensory or coordinating function and psychic symptoms. Nevertheless, tumors may occur in "silent" areas and produce no focal signs.

Glioma.—Gliomas are infiltrating invasive tumors derived from neuroglia. Usually a single tumor is found, but the ependymal cell glioma and certain other forms may be multiple. The size varies from an extremely small mass to

that of an entire cerebral hemisphere. The shape is generally spheroidal but may vary much with the situation, and is influenced by the usual, but not invariable, limitation by the pia mater. The glioma is most common in the brain but may occur in the cord and roots of cranial nerves. Certain histologic types have points of predilection. As a rule, the outline is not sharp and the tumor tissue fades gradually into the surrounding nerve substance, but sometimes a definite capsule is present. The consistence is about that of gray matter. The color, usually pale reddish-gray, may be darker red in a highly vascularized or a telangiectatic tumor, or it may be almost white in a poorly vascularized mass. Small hemorrhages are common, but large extravasations

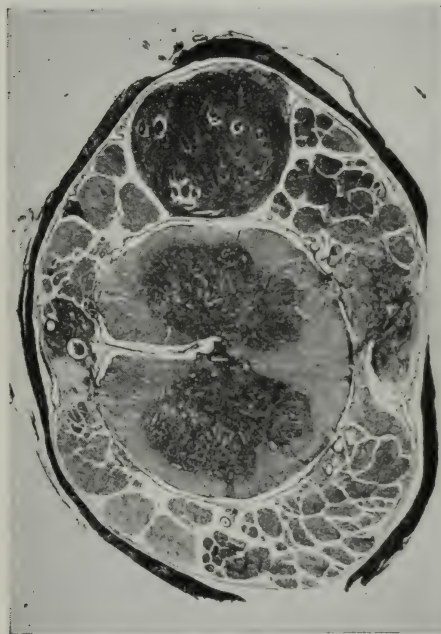


FIG. 430—Invasion of the spinal meninges by medulloblastoma. Bailey and Cushing's Classification of Gliomas.

with apoplectic symptoms may occur. Necrosis may be slight or marked. Cysts occur, filled with pale gray cloudy fluid which on fixation often solidifies into a gelatinous mass. Psammoma bodies may be found, calcification may be extensive, and even ossification is said to occur. Extension may be in the form of general enlargement, the tumor may break through the meninges and extend over the surface, or additional discrete masses, presumably metastatic, may be found.

Microscopically, the glioma may be uniform in cell type or show some variations. In the latter case it is usually diagnosed by the preponderant cell. In the differentiation of the primary neuroectodermal cells there are formed medulloblasts, spongioblasts, and neuroblasts, in addition to the precursors of pineal, choroidal and

ependymal cells. Through stages of further differentiation the neuroblasts produce the neurone, the spongioblasts produce the astrocyte, and the medulloblasts, in addition to producing oligodendroglia may apparently produce some spongioblasts and neuroblasts. On the basis of this scheme of differentiation Bailey and Cushing distinguish thirteen tumor types, representative of various cells found in the course of development of adult nervous system. Furthermore, they have shown that in a general way the less differentiated types of tumor grow more rapidly and are less favorable in their course than the more highly differentiated forms. The outstanding features given here are based upon the monograph of Bailey and Cushing.

The *medullo-epithelioma* is rare, is a rapidly growing invasive tumor composed of undifferentiated columnar cells, which tend to be arranged in canal-like form, somewhat resembling the original neural tube. The *medulloblastoma*

may arise in any part of the central nervous system, but is most often found as a rapidly growing tumor of the cerebellum in children. The cells have scanty cytoplasm, richly chromatic nuclei, numerous mitotic figures, and are usually in solid masses but may be arranged to form pseudo-acini and pseudorosettes. The cytoplasm is extended into a tail-like process which does not take the stains for neuroglia, nerve fiber or connective tissue; thus, the cell corresponds to the medulloblast. Spongioblasts, stainable by Hortega's fourth variant, with their blepharoplasts, are sometimes present. Neuroglia fibrils may differentiate and typical astrocytes may be found. Even large neuroblasts with their large vesicular nuclei are encountered. These tumors may extend widely over meningeal surfaces and the condition was formerly spoken of as meningeal sarcomatosis. Here the cells are uniformly small, undifferentiated cells. Rarely such masses are found without a primary lesion in the brain, are probably derived from meningoblasts and are to be called meningoblastoma. Lack of differentiation may be observed in retinal tumors, the retinoblastoma. The same is true of the sympathetic system, with the formation of sympatheticoblastomas.

In the pineal gland, tumors may be made up of spongioblasts of the pineal proparenchyma, the *pineoblastoma*, or of more highly differentiated cells resembling those of the pineal gland, the *pinealoma*.

Tumors of the ependymal group originate in or near the ependyma of the ventricles. Two forms of ependymal tumors are distinguished. The *ependymblastoma* shows an arrangement of cells into communicating masses. The cells are ependymblasts with blepharoplasts and long tails differentiated into neuroglia fibrils. The cells of the *ependymoma* are polygonal, without tails, but also contain blepharoplasts. Both types of tumor have a supporting connective tissue stroma (see Hirsch and Elliot).

The *neuro-epithelioma* is rare in brain or cord, but its prototype is common in the retina. The tumor is made up of primitive spongioblasts which tend to form many rosettes. The *neuro-epithelioma retinae* is more highly differentiated and less malignant than the retinoblastoma, and the rosettes are considered to be formed by primitive rods and cones.

The *spongioblastoma* is made up of more highly differentiated cells than those of the neuro-epithelioma. Two forms are described, the *spongio-*

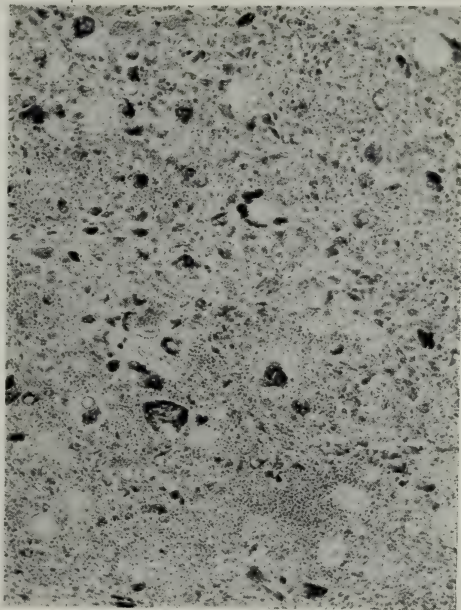


FIG. 431.—Spongioblastoma multiforme, showing marked variation in character of cells. Hematoxylin and eosin.

blastoma multiforme and the *spongioblastoma unipolare*. The *spongioblastoma multiforme* is the commonest of the cerebral gliomas and may be found anywhere in the central nervous system. It is usually single but may be multiple (see Globus and Strauss). It is usually poorly defined and highly invasive and some examples have been called sarcoma or gliosarcoma. The cells are usually without any regularity of arrangement, or are multiform as to outline and nuclei. The cytoplasm varies in amount and the cells may be spindle, polygonal or of other forms, including that of rather imperfect astrocytes. The nuclei vary in size, shape and chromatin content, the mitotic figures show numerous abnormalities. Multinucleated tumor cells are not infrequent. The blood vessels usually have thin walls but endothelial and fibrous proliferation occur, the walls may be hyaline and both thrombosis and rupture are common. Necrosis may occur in large areas and liquefaction may

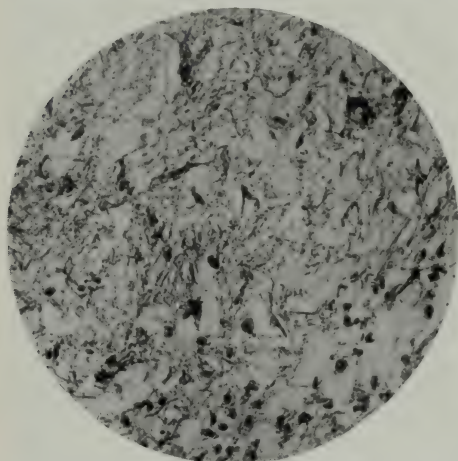


FIG. 432—Glia fibrils in *spongioblastoma multiforme*. Same specimen as Fig. 431. Phosphotungstic acid hematoxylin.

produce cysts sometimes lined by pseudo-epithelium made up of tumor cells. Tumor cells may be preserved around vessels in areas of necrosis so as to resemble perithelioma. Occasionally, the necrotic areas are partly organized by mesoblastic granulation tissue, but adult stroma is scanty. The invaded tissue shows various degenerations in nerve and glia cells. Bailey and Cushing regard the multiformity as due to progressive degeneration and regeneration.

The *spongioblastoma unipolare* is rare and is made up of unipolar spongioblasts with a few bipolar forms. Numerous fibrils are present which

stain poorly by phosphotungstic acid hematoxylin.

The *astroblastoma* is uncommon. It is made up of loosely arranged cells, which are large, rich in cytoplasm, sometimes triangular, often multinucleated. The cell processes are not dendrites and do not stain as glia fibrils. More highly differentiated but difficult to distinguish from *astroblastoma*, is the *astrocytoma*, which may be protoplasmic or fibrillary. The protoplasmic type is poorly vascularized, subject to necrosis and cyst formation and is composed of loosely arranged protoplasmic astrocytes without glia fibrils. The fibrillary type is more common and has much the same appearance except that these cells produce many fibrils, extensive and interlacing. The existence of the *oligodendroglioma* is doubtful, it is incompletely studied and is said to be made up principally of oligodendroglia cells and their scanty processes.

As indicated in the chapter on tumors, the term *neuroblastoma* is now restricted to those rare tumors made up of neuroblasts. With the newer staining methods, most of the tumors formerly called *neuroblastoma* and

neurocytoma are found to be medulloblastomas. The true neuroblastomas are composed of bipolar neuroblasts, from which non-myelinated neurofibrils pass. There may be a fair connective tissue reticulum. The ganglioneuroma, rarely if ever, occurs in the brain, and is found principally in connection with cranial or spinal nerves. The type cell is a large, practically mature, ganglion cell, from which pass fibers with or without myelin sheath. The cells often contain Nissl granules and may be multinucleated.

The *papilloma chorioideum* is a papillary tumor-like mass which springs from, and is made up principally of, cells of the tufts.

Meningioma (Dural Endothelioma).—Although other investigators had pointed the way, the work of Mallory and of Cushing has clearly indicated that the tumor commonly known as the dural endothelioma originates in the arachnoid villi, which project into the dura along the course of the venous sinuses and their tributaries. Owing to the fact that the cells in the villi are actively phagocytic, they are considered by many to be mesothelial. Because in their tumor growth they produce fibroglia and collagen fibers and occasionally elastic fibers, Mallory regards the cells as fibroblastic in character. The meningioma is usually single, but may be multiple, and although it may be situated in any place where arachnoidal villi are found, is most common in the superior and frontal regions. It may be flat and superficial or more commonly is spheroidal. Its point of attachment to the dura is often torn away and difficult to identify when the dura is stripped from the brain. It is well defined, does not invade the brain but pushes it away, has a thin capsule, is easily shelled out, and often shows a somewhat lobulated surface. The consistency varies from moderate firmness to great density. The cut surface is firm or dense, usually pale, sometimes has a "watered silk" appearance, with moderate or little vascularization, may be necrotic and may show small hemorrhages. The surrounding brain may show encephalomalacia, and sometimes edema extends for several centimeters beyond the tumor. The overlying bone is usually normal, but there may be hyperostosis both internally and externally. In these cases tumor cells may be found in the lacunæ and canaliculi, and these small masses may fuse so that the original tumors extend through the tables.

Histologically, there are usually sheets of cells, oval, circular and even spindle form, with clear cytoplasm and oval vesicular nuclei. These may be arranged in concentric whorls slightly resembling cancer pearls but without

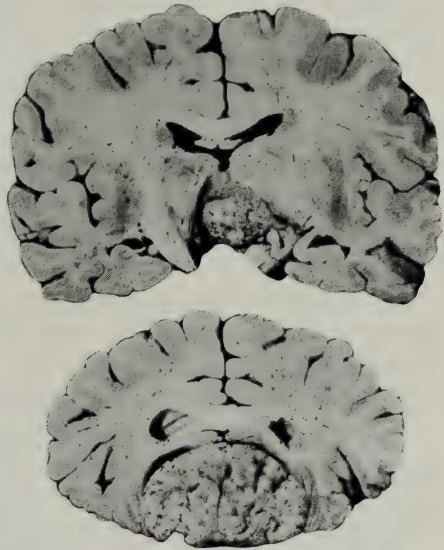


FIG. 433.—Two levels of meningioma of base of brain. Note absence of invasion.

keratinization. There is some resemblance to the cellular arrangement of the arachnoid villi. The stroma varies in amount and may divide the tumor into pseudo-alveoli. In other cases the microscopic picture is like that of fibroma or fibrosarcoma, with many fibrils and few nuclei, and the distinction from fibrous tumors depends upon finding more richly cellular fields and upon the position of the tumor. Vascular supply is variable in amount and character. Mitotic figures may be frequent in the more cellular tumors, but are usually absent from the fibrous types. Psammoma bodies are not uncommon.

Meningiomas are much less frequent in the spinal canal, where they usually take origin from the arachnoid where a nerve root passes through.

Primary sarcoma, since the detailed study of gliomas has been made, is now known to be extremely rare. The diffuse meningeal sarcoma is now regarded as an extension from the medulloblastoma or as a primary meningeoblastoma. Sarcomas may arise from the mesoblastic tissue of the central nervous system or from the bones.

Angioma.—These masses may be capillary or cavernous. They occur in the cranial and spinal cavity and usually originate in the meninges. Only rarely do symptoms occur except as a result of hemorrhage. As with angiomas of the skin and liver they represent embryonal malformations, but may rarely be a part of a more complex hamartomatous condition (Campanacci).

Melanoma.—This tumor arises from chromatophores in the pia mater of the brain or cord, although one case is reported in the fourth ventricle, may invade the nerve substance but tends to extend over the meninges, and practically never shows distant metastases. The cells may be round or spindle form and the amount of pigment variable (Omodei-Zorini).

Lipoma, fibroma, chondroma, chordoma, are occasionally found in the central nervous system and do not differ in character from similar tumors found elsewhere.

Cholesteatoma, or pearly tumor, usually occurs at the base of the brain in either intra- or extradural position, but may occur in cerebellum, cerebral ventricles or in the middle ear. Ordinarily the tumor is small, but may attain a diameter of several centimeters. It may be a spongy mass or cystic, has a pearly luster, is adherent to the meninges and contains fatty material, somewhat like sebum, made up of various fatty and lipid substances. Cholesterol is usually present in large amounts but may be absent. Histologically, the outer layer, stratum durum, is made up of connective tissue, the intermediate layer, stratum granulosum, is made up of epithelial cells, and the innermost layer is made up of flat cornified epithelial cells (Bailey). Sometimes hair follicles may be found and the growth may be dermoid in type. The epithelial growth may become carcinomatous (Ernst). The cholesteatoma may be regarded as originating in hamartomatous epithelium.

Dermoid cysts with fairly high degree of differentiation may be found at the base of the brain but are uncommon (see Rand).

Epithelial Tumors.—In addition to those mentioned above, and the papilloma chorioideum, the epithelial tumors of importance are those described in

the chapter on ductless glands as arising in remnants of the pouch of Rathke and in the pituitary gland. It is rare for any epithelial tumor in the cranial cavity to become an outspoken carcinoma.

Tumors of the spinal canal may be grouped as (a) those which originate in the bones, and extradural and intradural tumors, and (b), those which originate in the cord itself. Various tumors may be primary or secondary in the bones and either compress or invade the cord. Extradural tumors are usually metastatic. Intradural tumors include the meningioma, the meningoblastoma and extensions from cerebral medulloblastoma, as well as benign tumors, especially neurofibroma of the spinal roots. The principal tumor of the cord itself is some form of glioma. The symptoms are referable to local pressure or invasion by the tumor, but Stookey points out that the early symptoms of extradural tumors may be masked by the diffusion of pressure through the spinal fluid.

Tumors of Cranial Nerves.—With the exception of the acoustic nerve, tumors are uncommon, although Cushing reports meningiomas of the acoustic, of the trigeminal and of the optic nerves. Great interest has centered about the tumors of the cerebellopontine angle. These may be of almost any variety but are usually either meningiomas or more especially neurofibromas of the acoustic nerve (see Cushing). The latter usually originate in that part of the nerve within the porus acusticus and grow inward to be in relation to the pons, the upper surface of the cerebellum and the lower surface of the cerebrum. They are usually firm, nodular or smooth, pale tumors, small when they are still in the porus, or attaining diameters of several centimeters in the posterior fossa. Microscopically, they are usually a mixture of fibrous tissue, sometimes with parallel rows of nuclei (palisade arrangement) and a loose network of vesicular cells. Cells resembling ganglion cells are sometimes found, which are probably fibroblasts. Glia fibrils may be found, which are either remnants of, or perhaps a proliferation of, the supporting glia of the nerve to be found normally for several millimeters of its length before a true endoneurium is encountered.

As a rule, tumors of the nervous acusticus are single. They may be bilateral and associated with a more widespread neurofibromatosis. Multiple meningiomas may accompany tumors of the nervus acusticus and multiple herniation of the dura is not infrequent. All these facts suggest that there is some developmental condition that predisposes to tumors of all these groups (see Winestine).

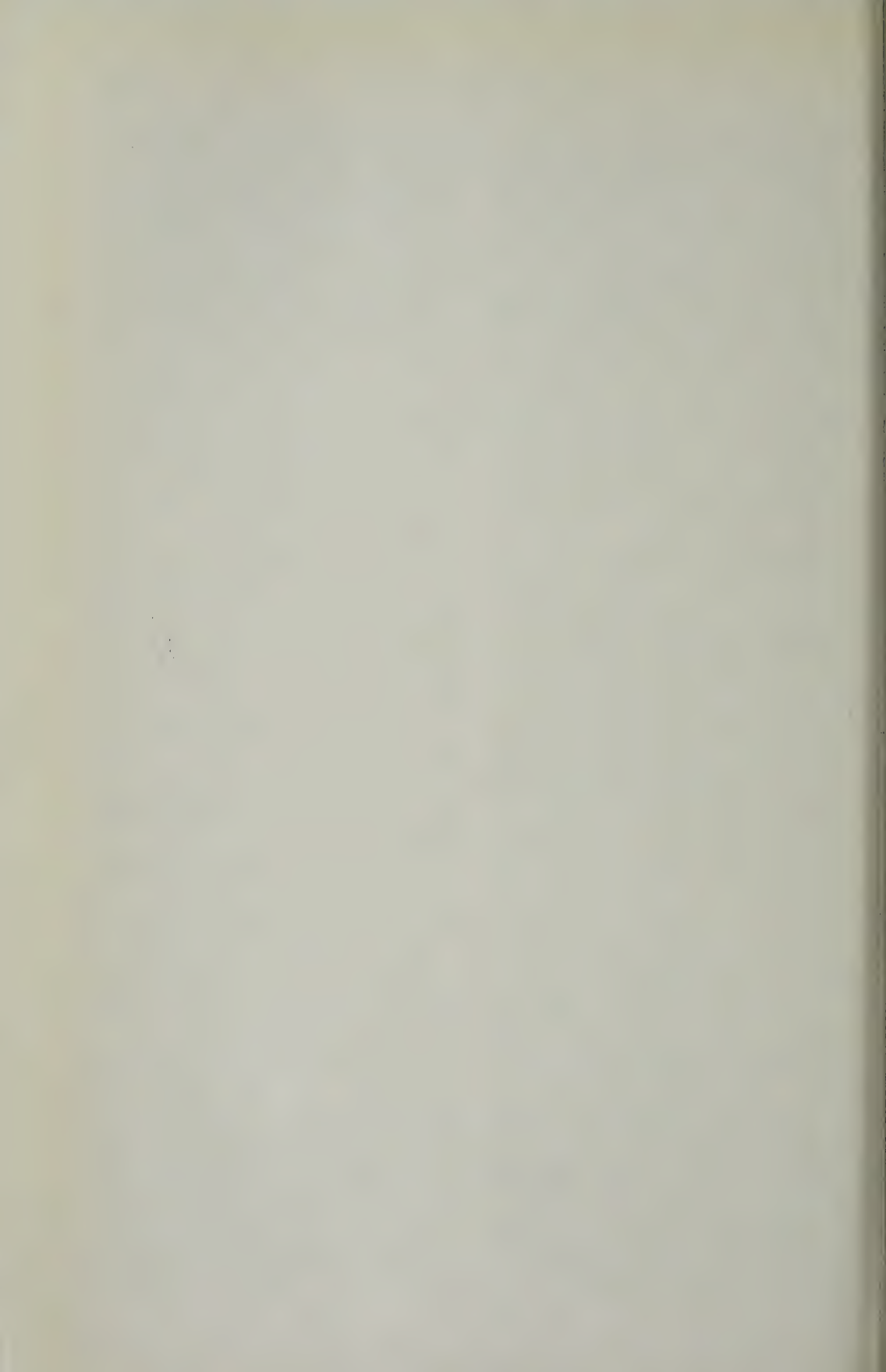
Tumors of Peripheral Nerves.—The neuroma, multiple neurofibromatosis of von Recklinghausen, amputation neuromas, and the tumors of the sympathetic system have been discussed in the chapter on tumors.

Secondary tumors may occur in any part of the central nervous system from primary malignant tumors elsewhere. They may produce surrounding edema, softening, inflammation or hemorrhage. Pressure symptoms are variable. The focal symptoms depend upon the situation.

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